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Newer Modalities in the Treatment of Type 2 Diabetes Mellitus: Focus on Technology

Alan B. Schorr

Abstract

This chapter will focus on the technological advances for individuals with Type 2 diabetes mellitus and their effect on treatment, control of blood glucoses and possible improvement in lifestyle and decreasing complications. This is a general overview of technological improvements and not an outline for specific patient care. Various technologies will be discussed and the outlook for future improvements outlined.

Keywords: CSII-continuous subcutaneous insulin infusion, CGM-continuous glucose monitoring, HbA1C, MDI-multiple dose injection, smart pen

1. Introduction

During the past 30 years, there has been significant advances in technology for the treatment of patients with Diabetes Mellitus. Most of these advances have focused on patients with Type 1 diabetes mellitus. The perception has been that individuals with Type 2 diabetes mellitus have not needed these advances or that they are not appropriate for a population that does not always require insulin.

Type 2 diabetes mellitus is a disease which is multifactorial: linked to metabolic derangements, Obesity, dietary behavior along with lifestyle issues particularly those individuals who are Sedentary [1, 2]. Given these factors, technology has been considered as adjunct therapeutic modalities to use in addition modification of diet, education, medications and lifestyle changes.

2. Insulin pump therapy (CSII)

Continuous Subcutaneous Insulin Infusion (CSII) has been utilized since the 1970s for the treatment of Diabetes Mellitus. The first insulin pumps were extremely large and bulky. Dr. Arnold Kadish devised a backpack insulin pump in the 1960s, but it proved to be less than optimal for everyday use. Dean Kamen in the late 1970s developed a more practical portable insulin pump which was eventually produced by Baxter called the Auto Syringe. This was the initial insulin pump that this author utilized in the early 1980s. Insulin pumps have evolved significantly over the past 40 years becoming smaller, more precise in the delivery of insulin doses and more reliable than their older versions [3]. During the 1980s to early 2000s,

there were several companies providing insulin pumps to the public. Due to varying factors, these companies ceased production and in the late 2000s, there were only 4–5 companies in the US. As of 2018, there are only three large companies still functioning in the USA: Medtronic Diabetes, Omnipod and Tandem. There are several more companies in Europe that are providing insulin pumps. In the future there may be additional entries into the US market from other companies. Patch pumps are of particular interest to many individuals with DM.

The use of continuous subcutaneous insulin infusion as a primary therapy for Type 2 DM patients has been investigated for the past 40 years. It has been utilized in various patient groups, including those who have newly diagnosed Type 2 DM. It is noted that individuals with Type 2 DM have poor to average control [4].

Multiple uncontrolled studies from 2008 to 2013 evaluated insulin pump therapy (CSII) in patients with Type 2 diabetes mellitus. The various studies indicated switching to CSII therapy led to improved glucose control generally, reduction in daily insulin doses compared with conventional Multiple Dose Injection therapy (MDI) and improved patient satisfaction [5]. These studies were conducted in various entities- Clinical Research Centers, Hospital outpatient clinics and small private outpatient offices.

Random Clinical Trials evaluating the efficacy of CSII therapy versus conventional MDI have been conducted and published since 1991 [6–13]. Many of these earlier studies were shorter ranging from 16 to 32 weeks and showed minimal benefit of one modality over the other.

The OpT2mise trial included a large heterogeneous population noted significant benefit compared with MDI with lower HbA1C levels, decrease in insulin requirement and no significant change in weight and no change in hypoglycemic events. This was a large scale multi center international trial which compared the efficacy of CSII therapy to intensive MDI therapy in patients who were not able to reach HbA1C goals despite intensified MDI regimens. This was a randomized parallel group study encompassing a run-in phase, 6-month randomized phase and a 6-month continuation phase. To continue in the trial a minimum of 3 measurements of glucose per day was required [14].

The study noted that CSII therapy significantly improved blood glucoses in patients when compared with MDI regimens (~ mean difference was 0.7%). There was a 20% decrease in the total insulin dose per day with little or no change in hypoglycemic events or weight gain. Additionally, these results also indicate that selection of the proper individual for CSII treatment is paramount. The study also noted that ~ 38% of patients in the CSII treatment arm had mild cognitive impairment. Patients with such impairments can successfully implement CSII therapy with proper training and education.

This landmark study of CSII in Type 2 DM individuals does have some notable limitations. Patients with insulin resistance utilizing greater than 220 units per day were excluded. This is a large population which is increasing, and further large studies need to be considered. The study did not include individuals utilizing concentrated forms of insulin (U-200 and U-500).

Additionally, the study does not take in account the availability of continuous glucose monitoring and depended on serum blood glucose (SBG) monitoring. With the advent of flash glucose monitoring and advances in continuous glucose monitoring (CGM) discussed in another part of this chapter, additional studies comparing CSII and MDI in these patients may be warranted.

At present, the CSII systems available for patients with Type 2 DM include pumps with sensor combinations that have the ability to suspend delivery if the sensor notes low glucose [15].

These systems are presently the only ones approved for patients with Type 2 DM.

Future advances in CSII use for Type 2 DM could include the use of the hybrid closed loop system which is now available for Type 1 DM individuals. The Medtronic hybrid closed loop system is the only one currently available. This system automatically adjusts the basal delivery every 5 minutes based on sensor readings. The system attempts to maintain glucose levels to an assigned target [16]. This form of CSII therapy functions with two different modes: Auto mode which uses an algorithm to respond to glucose levels. Manual mode is similar to previous pump-sensor combinations and requires preset basal rates by the individual in conjunction with his/her physician. Both systems still require manual meal bolus (MB) administration and manual correction for consistently elevated glucoses. Other companies are presently testing their versions of closed loop hybrid systems which may be available in the near future [17].

Patients with extreme insulin resistance have been at a disadvantage utilizing CSII therapy due to the restricted capacity of the pumps (either 180 units, 200 units, 300 units). One company in Europe has developed small insulin pumps with 500 unit and 800-unit capacity though this system is presently not available in the United States [18]. Physicians have resorted to utilizing U-500 in the pumps to decrease the frequency of site and pump changes. Several studies have noted the efficacy and improvement in quality of life with the use of U-500 in CSII therapy [19, 20]. Additional attempts to improve glucose control, quality of life, decreasing insulin requirements for Type 2 patients has led to use of so called “double pump” systems, utilizing insulin in 1 pump and pramlintide in an additional pump. Results in a small non-double-blind placebo-controlled observational study indicated a 10–20% decrease in insulin requirements, improvement in glucose control, weight loss and significant improvement in quality of life [21]. Limitations included the ability to obtain supplies for two separate pumps and utilization of pramlintide as this medication in vials was discontinued by the manufacturer at the direction of the FDA.

CSII therapy has been considered an improvement over traditional MDI therapy due to multiple factors: (1) There is predictable absorption of insulin. MDI which traditionally requires injection of larger doses of insulin will form a depot and generally less efficacious in absorption and metabolic activity compared with CSII which involves smaller volumes [13]. Both the basal rate and meal bolus with CSII can be utilized with more precise insulin increments (tenths or hundredths of units). (2) Patients using CSII therapy appear to have increased satisfaction with this form of insulin therapy compared with traditional MDI injections. Based on personal observation and previous studies, patients find CSII more convenient for their lifestyle, easier to utilize after being trained and more likely to adhere to the treatment regimen. There is less likelihood of omitting (forgetting) their dose of insulin as compared with MDI. Peyrot et al. noted that patients record regular omission of insulin injections [22]. Personal observation of patients within my practice regularly indicates individuals utilizing MDI regularly admit missing meal time insulin injections. Those using CSII therapy note that since the insulin pump is attached and readily available, along with various alarm reminders missing doses is minimal. (3) The ability to download information from insulin pumps to websites (each pump has its own download capability which can cause increase work for the physician) can facilitate more efficient data collection and an ability to change the treatment regimen between patient visits.

Given the advantages of CSII therapy over MDI therapy, it would appear that CSII therapy should be considered for individuals with Type 2 DM as it is now considered for patients with Type 1 DM. However, cost effectiveness in several health systems has not been completely demonstrated. Current policies in many health systems are varied and the ability for patients to obtain access to CSII therapy may be limited.

3. Continuous glucose monitoring (CGM)

Continuous glucose monitoring or CGM was first available for research projects in the 1970s.

Miles Laboratories in the late 1970s developed the Biostator which was large, bulky and required IV access. It had little use in everyday clinical practice, due to its size, need for constant supervision, IV access and waste of blood in order to measure glucose levels [23, 24].

In 2002, the GlucoWatch Biographer was introduced. It was shaped like a watch, similar to the Apple Watches of today. It adhered to the skin and used interstitial fluid to measure glucose levels every 10 minutes for 13 hours. [25]. See **Figure 1**.

Due to its process reverse iontophoresis, the GlucoWatch had significant drawbacks. It was painful for many individuals, had accuracy issues and was difficult particularly in warmer climates with individuals sweating. The Autosensor, which was replaced every 13 hours had caused skin changes and irritation in many patients. Eventually the GlucoWatch was discontinued in late 2007. It did, however, pave the way for the CGM systems of today.

The current CGM systems use an enzymatic modality that reacts with interstitial fluid glucose and transfers it to an electrode. The electrical current that is generated is then relayed to a reader via Bluetooth wireless or an app on a smart phone which displays the results to the individual. The data can also be downloaded to a computer. Additionally, the information can be stored to the cloud and relayed to the physician or caregiver via a secure website [26].

It must be noted that interstitial glucose measurements can lag 5–15 minutes behind blood glucose measurements particularly if there is rapid variability [27, 28]. Previously, CGM systems required calibrations twice per day which introduced a perceived limitation particularly for individuals who wished to limit “finger sticks” as an incentive to move to CGM systems.

The newer versions of CGM to include the DEXCOM G6, Guardian 3 and a flash form of CGM, the FreeStyle Libre (10-day and 14-day systems) have decreased the necessity of frequent calibrations.

In recent years, there have multiple studies with CGM involving individuals with Type 2 diabetes mellitus. The focus has been efficacy, the effect of CGM



Figure 1.
Gluco Watch Biographer 2.

with regards to hypoglycemia and glucose variability [29]. A study conducted by Vigersky et al. with patients utilizing diet, lifestyle vs. other combinations of oral agent therapy with or without basal insulin noted a reduction of mean unadjusted HbA1C of 1.0% vs. 0.5% in the SMBG group at week 12 and 0.8% vs. 0.2% at week 52. This occurred without intensification of medication or an increase in hypoglycemic episodes [29]. An additional study by Fonda et al. noted even an intermittent use of CGM may be appropriate for motivating individuals or helping to avoid “burnout” [30, 31].

The DiaMonD study (Daily Injections and Continuous Glucose Monitoring in Diabetes) study was a 6-month randomized control trial that compared the effectiveness of CGM to SMBG in individuals using MDI (multiple daily injections). This included both Type 1 and Type 2 DM patients. The results of the 6-month trial for Type 2 patients was published in 2017 and noted the following: Type 2 DM individuals after 24 weeks using CGM had an average 0.8% reduction in HbA1C levels compared with baseline. Those with higher A1C levels noted the greatest reduction with a group starting with A1C levels greater than 9.0% noting an average 1.4% reduction from baseline. Those using CGM had an increase in time spent in the target range compared with the control group (those only using SMBG). The A1C reductions occurred with minimal changes in insulin doses, little or no change in regimen or addition of non-insulin medications [32].

CGM has also been useful in recognizing previously undetectable episodes of hypoglycemia. Studies conducted by Zick et al.; Pazos-Couselo et al.; Klimontov and Myakina all noted a significant higher percentage of hyperglycemic episodes observed with the use of CGM compared with SMBG use.

The use of CGM particularly in older individuals utilizing insulin therapy has noted significantly higher incidences of nocturnal hypoglycemia compared with those utilizing only CGM. This indicates that CGM can be useful in high-risk Type 2 DM populations such as the elderly, those with special needs and individuals that have difficulty utilizing HGM such as severe arthritic conditions, vascular issues, etc. [33–36].

CGM is also a tool to assess glucose variability. This has become important in outcome measurements recently in addition to the standard A1C levels. The INITIATION study which tested an insulin initiation algorithm in Type 2 DM patients used CGM in 78 patients who were followed for 24 weeks. The results noted that insulin initiation reduced hyperglycemia but not glucose variability [37, 38]. The FLAT-SUGAR study which randomized 102 patients who were on metformin and basal/bolus insulin to either maintenance with basal/bolus therapy for changing the basal insulin to GLP-1 therapy. The drug used with this study of 26 weeks was exenatide BID. Using CGM it was noted that the GLP-1 group had lower variability of glucose as measured by the coefficient of variation. Of note with this study, A1C levels or episodes of hypoglycemia did not change significantly between the treatment groups [39–41].

These studies and others both past and presently being conducted have shown the CGM use in patients with Type 2 DM can improve A1C levels, detect risk of hypoglycemia which is not clinically apparent, particularly nocturnally and may be able to assess and address glucose variability.

There are two forms of CGM presently available for use in clinical practice: (1) Professional CGM and (2) Personal CMG. Professional CGM is placed in the physician office and does not require the patient to obtain or purchase a system. It is a blinded system in many instances, that is, the patient has no access to the results immediately and must wait for the CGM to be downloaded in the physician's office, analyzed and then informed of the results. These systems can be worn for 3, 7 or 14 days, though generally the 7- or 14-day systems are more popular

today. The systems available today in the United States for professional use are: the DEXCOM Professional system, the FreeStyle Libre Pro system, Medtronic iPro 2 system. Most of these systems do require additional calibration. Once the study is completed, the data is downloaded to either the cloud or a specific program on the computer and then can be reviewed by the physician or allied health provider in conjunction with the physician and then shared with the patient. The blinded system can be helpful in regards that the patient is not responding during the time of the study but continuing their usual habits to include diet, activity and medications. Reimbursement for use of Professional CGM has improved over the past several years particularly in the United States. Requirements as the reporting of CGM results can vary among the different health plans which can lead to limitations in its use.

Personal CGM consists of an individual obtaining a system which is unblinded and provides blood gluces every 5+ minutes for DEXCOM and Guardian 3 systems. These systems are placed subcutaneously and have alarms with notify the patient when certain patterns or thresholds are detected. There are multiple threshold alarms, rate of change alarms, predictive alarms. Predictive alarms are useful in that it permits the individual to take preventative action rather than corrective action. However, the downside of these alarms is that there can be false positives and false negatives. This can lead to so-called “alarm fatigue” [42]. Individuals will in many instances either ignore or silence the systems due to the multitude of alarms. In some cases, they will abandon CGM altogether. The DEXCOM G5–6 system is the only CGM device at present that is approved by the FDA for a non-adjunctive indication. It can be considered a therapeutic CGM, allowing individuals and physicians to modify therapy based solely on the readings and trends.

The FreeStyle Libre system utilizes a flash monitoring system. It is placed like the other CGM systems subcutaneously but provides glucose results when the CGM is scanned. Thus, the results are intermittent depending on the frequency of scanning by the patient [43]. The newest of the FreeStyle Libre systems, the 14-day unit improves over the older 10-day system with a 1-hour warm up period compared with 12 hours. Several randomized controlled trails note that the use of flash CGM with the Libre system reduced hypoglycemia, increased the time in target range and reduced glucose variability [44, 45] Studies and personal observation have also shown higher device utilization. This may be due to the simplicity of application and ease of use. The use of this system in increasing and may prove to be an asset particularly in individuals who may not need the sophistication of the more complex CGM system but want the benefit of CGM and not have to consistently perform SMBG or finger sticks.

Additional studies in Europe have shown the cost effectiveness of CGM in the management of patients with Type 2 DM receiving intensive MDI regimens and also improvement in the detection and avoidance of hypoglycemia in individuals with Type 2 DM [46, 47].

Another technological advance in CGM has been the development and approval of the implantable CGM system by Senseonics called the Eversense System. The system consists of an implantable cylindrical sensor 3.5 mm × 18.3 mm in size. This is implanted by the physician every 90 days in the upper arm area under the skin. When the system is activated, it measures interstitial glucose levels every 5 minutes. The data is transferred to a battery powered transmitter that is worn externally over the sensor. The external transmitter also provides alerts similar to other CGM systems for impending hypo or hyperglycemia. The transmitter needs to be recharged for ~15 minutes every other day. The sensor is explanted, and a new sensor implanted every 90 days. A 180-day sensor is being developed for the future.

Several studies have shown the accuracy and acceptability of an implantable glucose sensor. The PRECISE and PRECISE II studies noted that the Eversense

system was safe and provided accurate glucose results during the 90-day sensor life [48, 49]. An additional study in the UK and Germany comprising a subgroup of individuals in the PRECISE trial who were administered quantitative psychosocial assessments that included the Diabetes Distress Scale (DDS), CGM Impact Scale and a bespoke device satisfaction questionnaire. The results of the sub study indicated that an implantable CGM was acceptable to most of the participants and the majority of users both first time to CGM or previous CGM users would continue to use an implantable CGM to manage their glucoses and DM more effectively [50].

As the accuracy of CGM improves, particularly in the hypoglycemia range, the acceptance should also increase. However, at this time, CGM still does not, in the eyes of the regulatory agencies substitute fully for conventional SBGM. With continued development and use, it appears that eventually CGM, with or without CSII therapy will become the “standard of care” for both Type 1 and Type 2 diabetes mellitus.

4. Smart pen systems

Most individuals with DM, particularly Type 2 DM, who utilize insulin therapy are using insulin pen systems to deliver their daily insulin dose. Previous administration of insulin via syringe and vial has been difficult to administer and master. Additionally, accuracy of dose has been questioned. Insulin pens are one of the most widely used devices worldwide in DM treatment and care [51].

A recent review of the literature and meta-analysis noted that insulin pen devices noted improvement in patient adherence and persistence with their treatment regimen. Hypoglycemia was noted to be reduced, with a possible improvement in dose accuracy in pen devices. However, these studies were limited, and the authors of the meta-analysis recommended additional larger scale studies [52].

Additionally, there is the issue of documentation of insulin doses. Many patients do not record the time and dose of insulin consistently. Many will state that they took their insulin with meals, nighttime, for correction of their glucose, etc. but will not be able to provide accurate documentation. Therefore, this can be a significant barrier to glycemic control. Guidelines developed by various organizations make no mention of the need to record insulin dose administered and timing of injection whether the patient uses pen or syringe/vial.

In December 2017, the FDA approved the first smart pen system in the US. This insulin pen system records the dose of insulin and time of injection and transmits the data via Bluetooth to a mobile application that is downloaded on the patient’s smart phone. The mobile app has the capability of dose calculation and less than whole number units which conventional insulin pens are not able to deliver.

It can also inform the individual how much insulin is on board (IOB) similar to CSII devices. This data is stored on the individuals’ smart phone and can be brought easily to the clinical visit for analysis by the physician/health care provider.

There may an additional entry in this area. Bigfoot Biomedical is developing an insulin smart pen that will connect to the FreeStyle Libre system. It will be controlled with a mobile app and hopefully adjust long and short acting insulin doses without manual input [53].

The benefits of a smart pen system in the treatment of individuals with DM can be summarized as follows:

1. Improvement in poor adherence to the treatment regimen and omission of insulin doses.

Having the data readily available and reminders on their phone can provide an extra incentive to be more compliant with their regimen.

2. Improvement with the risk of insulin dose errors. Access to dosing and timing of insulin can facilitate more accurate doses and limit the risk of accidental overdose or under dosing.

This being a relatively new technology, these devices will need to demonstrate improvement in clinical and QOL (Quality of Life) outcomes, cost effectiveness, ease of training and use. However, many of the technologies discussed above have underwent the same scrutiny. The issue of cybersecurity as with any connected DM devices will need to be resolved to maintain patient confidentiality and integrity of the data. Smart pens may be an alternative to individuals who do not want CSII therapy for a multitude of reasons but would like to intensify their regimen and have access to appropriate dosing and timing of insulin to improve their glucose control.

5. Mobile and computer applications (apps)

Data Management software for diabetes has been available since the late 1980s to early 1990s. However, acceptance and adoption by both patients and physicians has been slow. The issues have been the ability to download or upload data with each device having its own set of software and cable connections. In many cases, physician offices had upwards of 6–10 different connections to obtain data from SMBG meters and other devices.

Over the past two decades, a number of innovations were developed that “streamlined” the ability to obtain data from patient devices. There has been an improvement in device connectivity with most devices now able to utilize Bluetooth technology thus eliminating the need for multiple cables or hubs. Additionally, smartphone technology has decreased the cost and complexity of data sharing. The use of automated uploads from devices to the “cloud” has allowed both patient and physician to have almost real-time access to data [53].

Proprietary cloud data platforms from multiple device manufacturers have been able to provide secure data and have developed common formats, easing the burden on physicians and their offices to maintain multiple programs. Also, many of the device companies, including those manufacturing SMBG devices have developed complex reporting capabilities that have been designated as Ambulatory Glucose Reports or Profiles.

The multitude of apps for the patient with DM has led to concerns of quality and safety. Apps available at both the Google Play store and Apple App Store may little or no oversight. A recent study in 2016 found that the majority of apps from the Google Play store did not meet the minimum requirements or did not work appropriately [54, 56] Additional studies are needed to fully investigate the efficacy and utility of mobile applications with regard to the treatment of individuals with Type 2 DM.

Another approach is to combine the mobile application, the cloud with a remote coaching system. Studies are now ongoing to assess the effect of individuals using a smart phone-based glucose monitoring system which automatically moves data to a secure cloud-based site [55]. A designated “diabetes coach” which is a health care provider (RN, NP or physician) then reviews the data several times per week and remotely connects with the patient to provide recommendations or discussion. Results are pending in these studies and hopefully preliminary results will be available in 2019. (Personal Observation).

The use of Artificial Intelligence (AI) in the treatment of patients with Diabetes is emerging and advancing at significant pace. Multiple programs are being developed to improve adherence and personalize the individual's regimen. Studies are ongoing to determine whether pattern recognition and the ability of machine learning can provide the patient with diabetes mellitus a unique, individualize model which is automated and can assist with predictions and decisions. At this time, AI cannot and does not substitute for patient – physician interaction and communication.

6. Conclusion

This chapter attempted to briefly outline the technological advances in the treatment of Type 2 diabetes mellitus. It is noted the technology has improved the quality of life, blood glucose control and possibly decreased the risk of complications. However, it must be pointed out to the reader that technology, no matter how advanced, does not substitute for personal interaction with patients. The ability to know your patient, his/her lifestyle, stressors, etc. plays an important role in designing the proper treatment regimen. Continued advances in technology will in the future make the physician/healthcare provider and the patient's ability to control his/her blood glucoses less complicated but ultimately the decisions to maintain diet, exercise, monitoring of glucoses remains with the individual.

Conflicts of interest

The author notes that he is a member of the DSMB and CEC for Medtronic Diabetes and serves on the Speaker's Bureau for Sanofi and Astra Zeneca.

Notes/thanks/other declarations

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References

- [1] Taylor R. Pathogenesis of type 2 diabetes: Tracing the reverse route from cure to cause. *Diabetologia*. 2008;**51**:1781-1789
- [2] Despres JP, Poirier P. Diabetes: Looking back at a look AHEAD-giving lifestyle a chance. *Nature Reviews Cardiology*. 2013;**10**:184-186
- [3] Heinemann L, Flemming GA, Petrie JR, Holl RW, Bergenstal RM, Peters AL. Insulin pump risks and benefits: A clinical appraisal of pump safety standards, adverse event reporting and research needs. *Diabetes Care*. 2015;**38**(4):716-722. DOI: 10.2337/dc15-0168
- [4] Pickup JC. Insulin pump therapy for type 2 diabetes mellitus. *Nature Reviews Endocrinology*. 2014;**10**:647-649. DOI: 10.1038/nendo.2014.142
- [5] Gentry CK, Cross LB, Gross BN, McFarland MD, Besterman WH. Retrospective analysis and patient satisfaction assessment of insulin pump therapy in patients with type 2 diabetes. *Southern Medical Journal*. 2011;**104**(1):24-28
- [6] Goa G-Q, Heng X-Y, Y-l W, et al. Comparison of continuous subcutaneous insulin infusion and insulin glargine based multiple daily insulin aspart injections with preferential adjustment of basal insulin in patients with type 2 diabetes. *Experimental and Therapeutic Medicine*. 2014;**8**(4):1191-1196
- [7] Wolf-McDonagh P, Kaufmann J, Foreman S, Wisotsky S, Wisotsky JAJA, Wexler C. Using insulin pump therapy in poorly controlled type 2 diabetes. *The Diabetes Educator*; **36**(4):657-665
- [8] Landau Z, Raz I, Weinstein J, Bar-Dayana CA. The role of insulin pump therapy for type 2 diabetes mellitus. *Diabetes/Metabolism Research and Reviews*. 2017;**33**:e2822. DOI: 10.1002/dmrr.2822
- [9] Raskin P, Bode BW, Marks JB, et al. Continuous subcutaneous insulin infusion and multiple daily injection therapy are equally effective in type 2 diabetes: A randomized parallel-group, 24-week study. *Diabetes Care*. 2003;**26**(9):2598-2603
- [10] Wainstein J, Metzger M, Boaz M, et al. Insulin pump therapy vs. multiple daily injections in obese type 2 diabetic patients. *Diabetic Medicine*. 2005;**22**(8):1037-1046
- [11] Parkner T, Laursen T, Vestergaard ET, et al. Insulin and glucose profiled during continuous subcutaneous insulin infusion compared with injection of a long acting insulin in type 2 diabetes. *Diabetic Medicine*. 2008;**25**(5):585-591
- [12] Weng J, Li Y, Xu W, et al. Short-term intensive therapy in newly diagnosed type 2 diabetes partially restores both insulin sensitivity and beta cell function in subjects with long term remission. *Diabetes Care*. 2011;**34**(8):1848-1853
- [13] Herman WH, Ilag LI, Johnson SI, et al. A clinical trial of continuous subcutaneous insulin infusion versus multiple daily injections in older adults with type 2 diabetes. *Diabetes Care*. 2005;**28**(7):1568-1573
- [14] Reznik Y, Cohen O, Aronson R, Ignacio C, Runzis S, Castaneda J, et al. Insulin pump treatment compared with multiple daily injections for treatment of type 2 diabetes (OpT2mise): A randomized open-label controlled trial. *Lancet*. 2014;**384**:1265-1272. DOI: 10.1016/S0140-6736(14)61037-0
- [15] Medtronic: Innovation Milestones. 2018. Available from: <https://www>.

medtronicdiabetes.com/about-medtronic-innovation.milestone-timeline [Accessed: 12-12-2018]

[16] Weaver KW, Hirsch IB. The hybrid closed-loop system: Evolutions and practical applications. *Diabetes Technology & Therapeutics*. 2018;**20**(Suppl 2):S2-S16. DOI: 10.1089/dia.2018.0091

[17] Trevitt S, Simpson S, Wood A. Artificial pancreas device systems for the closed loop control of type 1 diabetes: What systems are in development. *Journal of Diabetes Science and Technology*. 2016;**10**:714-723. DOI: 10.1177/1932296815617968

[18] Debiotech: Jewel Insulin Pump. Available from: https://www.debiotech.com/page/index.php?page=product_01&id=1&id_prod=40 [Accessed: 14-12-2018]

[19] Reutrakul S, Wroblewski K, Brown RL. Clinical use of U-500 regular insulin: Review and meta-analysis. *Journal of Diabetes Science and Technology*. 2012;**6**:412-420

[20] Lane WS, Weinrib SL, Rappaport JM, Hale CB, Farmer LK, Lane RS. The effect of long-term use of U-500 via continuous subcutaneous infusion on durability of glycemic control and weight in obese, insulin-resistance patients with type 2 diabetes. *Endocrine Practice*. 2012;**27**:1-18

[21] Schorr AB, Ofan R. Simultaneous use of two external subcutaneous pumps delivering insulin and SYMLIN: Use of a double-pump system. *Journal of Diabetes Science and Technology*. 2012;**6**:1507-1508

[22] Peyrot M, Rubin R. Validity and reliability of an instrument for assessing health-related quality of life and treatment preferences-the insulin delivery system rating questionnaire. *Diabetes Care*; **28**(1):33-39

[23] Clarke SF, Foster JR. A history of blood glucose meters and their role in self-monitoring of diabetes mellitus. *British Journal of Biomedical Science*. 2012;**69**:83-93

[24] Skyler JS. CGM-a technology in evolution. *Diabetes Technology & Therapeutics*. 2009;**11**:63-64

[25] The Diabetes Research in Children Network (DirecNet) Study Group. A randomized multicenter trial comparing the GlucoWatch Biographer with standard glucose monitoring in children with type 1 diabetes. *Diabetes Care*. 2005;**28**:1101-1106

[26] Klonoff DC, Ahn D, Drincic A. Continuous glucose monitoring: A review of the technology and clinical use. *Diabetes Research and Clinical Practice*. 2017;**133**:178-192. DOI: 10.1016/j.diabres.2017.08.005

[27] Rebel A, Rice MA, Fahy BG. Accuracy or point-of-care glucose measurements. *Journal of Diabetes Science and Technology*. 2012;**6**(2):396-411

[28] Vaddiraju S et al. Technologies for continuous glucose monitoring: Current problems and future promises. *Journal of Diabetes Science and Technology*. 2010;**4**(6):1540-1562

[29] Carlson AL, Mullen DM, Bergenstal RM. Clinical use of continuous glucose monitoring in adults with type 2 diabetes. *Diabetes Technology & Therapeutics*. 2017;**19**(Suppl 2):s-4-s-11. DOI: 10.1089/dia.2017.0024

[30] Vigersky RA, Fonda SJ, Chellappa M, et al. Short and long-term effects of real-time continuous glucose monitoring in patients with type 2 diabetes. *Diabetes Care*. 2012;**35**:32-38

[31] Sj F, Graham C, Munakata J, et al. The cost effectiveness of real-time continuous glucose monitoring

- (RT-CGM) in type 2 diabetes. *Journal of Diabetes Science and Technology*. 2016;**10**:898-904. DOI: 10.1177/1932296816628547
- [32] Beck RW, Riddlesworth TD, Ruedy K, Ahmann A, Haller S, Kruger D, et al. Continuous glucose monitoring versus usual Care in Patients with type 2 diabetes receiving multiple daily injections – A randomized Trial. *Annals of Internal Medicine*. 2017;**167**(6):365-374. DOI: 10.7326/M16-2855
- [33] Zick R, Peterson B, Richter M, Haug C. Comparison of continuous blood glucose measurement with conventional documentation of hypoglycemia in patients with type 2 diabetes on multiple daily insulin injection therapy. *Diabetes Technology & Therapeutics*. 2007;**9**:483-492
- [34] Pazos-Couselo M, Garcia-Lopez JM, Gonzalez-Rodriguez M, et al. High incidence of hypoglycemia in stable insulin treated type 2 diabetes mellitus: Continuous glucose monitoring vs. self-monitored blood glucose. *Observational prospective study*. *Canadian Journal of Diabetes*. 2015;**39**:428-433. DOI: doi.org/10.1016/j.jcjd.2015.05.007
- [35] Klimontov VV, Myakina NE. Glucose variability indices predict the episodes of nocturnal hypoglycemia in elderly type 2 diabetic patients treated with insulin. *Diabetes and Metabolic Syndrome: Clinical Research and Reviews*. 2017;**11**:119-124
- [36] Gomez AM, Umpierrez GE, Munoz OM, et al. Continuous glucose monitoring vs. capillary point-of-care testing for inpatient glycemic control in type 2 diabetes patients hospitalized in the general ward and treated with basal-bolus insulin regimen. *Journal of Diabetes Science and Technology*. 2016;**10**:325-329. DOI: 10.1177/1932296815602905
- [37] Kovatchev B, Cobelli C. Glucose variability: Timing, risk analysis, and relationship to hypoglycemia in diabetes. *Diabetes Care*. 2016;**39**:502-510. DOI: 10.2337/dc15-2035
- [38] Manski-Nankervis J-A, Furler J, Blackberry I, et al. Roles and relationships between health professional involved in insulin initiation for people with type 2 diabetes in the general practice setting: A qualitative study drawing on relational coordination theory. *BMC Family Practice*. 2014;**15**:20
- [39] Prostfield JI et al. Flat Sugar Trial Investigators: Glucose variability in a 26-week randomized comparison of mealtime treatment with rapid-acting insulin versus GLP-1 agonist in participants with type 2 diabetes at high cardiovascular risk. *Diabetes Care*. 2016;**39**:973-981. DOI: 10.2337/dc15-2782
- [40] Xu F, Zhao L-H, Su J-B, et al. The relationship between glycemic variability and diabetic neuropathy in type 2 diabetes with well controlled HbA1c. *Diabetology & Metabolic Syndrome*. 2014;**6**:139
- [41] Sartore G, Chilelli NC, Burlina S, Lapolla A. Association between glucose variability as assessed by continuous glucose monitoring (CGM) and diabetic retinopathy in type 1 and type 2 diabetes. *Acta Diabetologica*. 2013;**50**:437-442
- [42] Shivers JP et al. “Turn it off!”; diabetes device alarm fatigue considerations for the present and the future. *Journal of Diabetes Science and Technology*. 2013;**7**(3):789-794
- [43] Kudva YC, Ahmann AJ, Bergenstal RM, Gavin JR III, Kruger DF, Midyett LK, et al. Approach to using trend arrows in the FreeStyle Libre flash glucose monitoring Systems in Adults. *Journal of the Endocrine Society*.

2018;**2**(12):1320-1337. DOI: 10.1210/
js.2018-00294

2018;**20**(3):1-10. DOI: 10.1089/
dia.2017.0142

[44] Bolinder J, Antuna R, Geelhowed-Duijvestijn P, Kroder J, Weitgasser R. Novel glucose-sensing technology and hypoglycaemia in type 1 diabetes. A multicenter, non-masked randomized controlled trial. *Lancet*; **388**(10057):2254-2263. DOI: 10.1016/S0140-6736(16)31535-5

[50] Barnard KD, Kropff J, Choudhary P, Neuopane S, Bain SC, Kapitza C, et al. Acceptability of implantable continuous glucose monitoring sensor. *Journal of Diabetes Science and Technology*. 2017;**12**(3):634-638. DOI: 10.1177/1932296817735123

[45] Haak T, Hanaire H, Ajjan R, Hermanns N, Riveline JP, Rayman G. Flash glucose-sensing technology as a replacement for blood glucose monitoring for the management of insulin-treated type 2 diabetes: A multicenter open-label randomized controlled trial. *Diabetes Therapy*. 2017;**8**(1):55-73. DOI: 10.1007/s13300-016-0223-6

[51] Klonoff DC, Kerr D. Smart pens will improve insulin therapy. *Journal of Diabetes Science and Technology*. 2018;**12**(3):551-553. DOI: 10.1177/1932296818759845

[46] Bilir SP, Hellmund R, Wehler E, Li H, Munakata J, Lamotte M. The cost-effectiveness of flash glucose monitoring system for management of patients with type 2 diabetes receiving intensive insulin treatment in Sweden. *European Endocrinology*. 2018;**14**(2):80-85. DOI: 10.17925/EE.2018.14.2.80

[52] Lasalva P, Barahona-Correa J, Romero-Alvernia DM, Gil-Tomayo S, Castaneda-Cardona C, Bayona JG, et al. Pen devices for insulin self administration compared with needle and vial: Systematic review of the literature and meta-analysis. *Journal of Diabetes Science and Technology*. 2106;**10**(4):959-966. DOI: 10.1177/1932296816633721

[47] Adolfsson P, Rentoul D, Klinkenbiji PCG. Hypoglycemia remains the key obstacle to optimal Glycemic control-continuous glucose monitoring is the solution. *European Endocrinology*. 2018;**14**(2):50-56. DOI: 10.17925/EE.2018.14.2.50

[53] Baily TS, Walsh J, Stone JY. Emerging technologies for diabetes care. *Diabetes Technology & Therapeutics*. 2018;**20**(s2):78-84. DOI: 10.1089/dia.2018.0115

[48] Kropff J, Choudhary P, Neupane S, Barnard K, Bain S, Kapitza C, et al. Accuracy and longevity of an implantable continuous glucose sensor in the PRECISE study: A 180-day, prospective, Multicenter, pivotal Trial. *Diabetes Care*. 2017;**40**:1-6. DOI: 10.2337/dc16-1525

[54] Coughlin SS. Mobile technology for self-monitoring of blood glucose among patients with type 2 diabetes mellitus. *mHealth*. 2017;**3**:47-50. DOI: 10.21037/mhealth.2017.10.03

[49] Christianson MP, Klaff LJ, Brazg R, Chang AR, Levey CJ, Lam D, et al. A prospective Multicenter evaluation of the accuracy of a novel implanted continuous glucose sensor: PRECISE II. *Diabetes Technology & Therapeutics*.

[55] Brzan PP, Rotman E, Pajnikihar M, et al. Mobile applications for control and self-management of diabetes; a systematic review. *Journal of Medical Systems*. 2016;**40**:210. DOI: 10.1007/s10916-016-0564-8

[56] Huang Z, Soljak M, Boehm BO, Car J. Clinical relevance of smartphone apps for diabetes management: A global overview. *Diabetes/Metabolism Research and Reviews*. 2018;**34**:e2990. DOI: 10.1002/dmrr.2990