Glycemic Status Assessment

The advanced and performing technologies of glucose monitoring systems provide a large amount of glucose data that needs to be properly read and interpreted by the diabetology team in order to make therapeutic decisions as close as possible to the patient's metabolic needs. For this purpose, new parameters have been developed, to allow a more integrated reading and interpretation of data by clinical professionals. The new challenge for the diabetes community consists of promoting an integrated and homogeneous reading, as well as interpretation of glucose monitoring data also by the patient himself. The purpose of this review is to offer an overview of the glycemic status assessment, opened by the current data management provided by latest glucose monitoring technologies. Furthermore, the applicability and personalization of the different glycemic monitoring devices used in specific insulin-treated diabetes mellitus patient populations will be evaluated.

1. Introduction

Diabetes mellitus (DM) is a chronic metabolic disease with a rapidly growing prevalence. According to the International Diabetes Federation (IDF), a total of 463 million people aged 20–79 years are estimated to be living with diabetes, representing 9.3% of the global adult population. Type 1 diabetes mellitus (T1D) accounts for 5 to 10% of DM and type 2 diabetes mellitus (T2D) accounts for around 90% of all cases of diabetes [1]. Controlling glycemia in both T1D and T2D remains key to optimize the effectiveness of treatment, to reduce the risk of hypoglycemia, and prevent microvascular complications and reduce long-term risk of macrovascular diseases [2].

Structured self-monitoring of blood glucose and continuous glucose monitoring are valuable tools to improve glycemic control [3]. Several glucose monitoring systems are currently available for daily diabetes self-management ranging from self-monitoring of blood glucose (SMBG) to continuous glucose monitoring (CGM) up to the most emerging devices. Each has its own technology with specific strengths and limitations that can impact their usefulness and acceptability within specific patient populations. Furthermore, integrated insulin pump and glucose monitoring systems are now increasingly available [4].

ADA recommends to personalize glucose monitoring in each DM patient, according to the patient's characteristics, clinical needs, lifestyle, and treatment, by an accurate assessment of the different device technologies as well as integrated systems [4].

As far as advanced and performing technologies of glucose monitoring systems become available, the diabetes healthcare team faces an increasing number of available glucose data, that need to be properly read and interpreted, in order to get the best benefit for the patient. This is time-consuming and requires an adequate formation of the diabetes team, to make therapeutic decisions personalized on the patient 's metabolic needs, as much as possible. For this purpose, new parameters have been developed, to allow a more integrated reading and interpretation of data by clinical professionals and consequent homogeneous therapeutic decisions, to be shared by the whole scientific community. The use of time in range (TIR), glucose management indicator (GMI), and ambulatory glucose profile (AGP) are currently recommended [5]. However, CGM system not only provides a method of collecting and using glucose data for the diabetology team "perspective", but also for the patient "perspective". The new challenge for the diabetes community therefore consists in promoting an integrated and homogeneous reading, as well as interpretation of glucose monitoring data also by the patient himself. The final goal is to educate him/her to make therapeutic decisions as close as possible to his/her metabolic needs.

2. Glucose Monitoring Systems

2.1. Current Glucose Monitoring Systems

Self-monitoring of blood glucose (SMBG), based on capillary glucose testing, remains the longest-used method to monitor glucose levels and to maintain glycemic control in insulin treated DM patients [6].

SMBG devices are ultraportable with a good accuracy and sensitivity but only provide a snapshot of the glucose level at one specific point in time. The requirement to perform a fingerstick to obtain a blood sample can be time consuming, inconvenient, and painful, consequently leading to poor compliance thus limiting the potential benefits of SMBG [7]. Moreover, long-term trends in glucose fluctuations as a result of insulin therapy, diet, and lifestyle choices are not accurately reflected [8].

SMBG technology is constantly evolving and may have different advanced technologies up to SMBG device with automated bolus calculator with the goal to suggest patients the dose of insulin for the meals; there is evidence of an improvement in self-decision and in glycemic control, in patients using SMBG with this technology [9][10]. Several data shows that the automatic bolus calculator built into the glucometer is effective in improving blood sugar control and preventing hypoglycemic episode [11]. In addition, the evolution of mobile technology led to development of smartphone applications related to the use of image processing technology, e.g., GoCARB system, and voice recognition technology, e.g., VoiceDiab system, that recognize meals and provide decision support for prandial insulin dosage [12].

Over the past few years continuous glucose monitoring (CGM) has changed the way to monitor blood glucose. This technology provides a continuous measurement of glucose concentrations in the interstitial fluid as a way to optimize glucose control by keeping levels in their target in range for a longer period of time, thereby improving HbA1c. CGM systems consist of a disposable sensor that measures glucose concentration and can be inserted or implanted subcutaneously, and an external transmitter that stores glucose values and sends the values to a receiver as standalone or integrated on insulin pump or smartphone. The sensor is functioning from a minimum of 7–14 days for the inserted subcutaneous sensor to a maximum of 180 days for the implanted subcutaneous sensor [13]. The glucose data are either manually scanned or wirelessly transmitted to a nearby receiver to display the readings. Patients and their diabetology team are able to assess the glucose profile, which helps them to make appropriate decisions about therapy, diet, and physical activity [8].

Three types of CGM systems are now available: realtime CGM (rt-CGM), retrospective CGM (r-CGM), and intermittently scanned CGM (is-CGM) or flash glucose monitoring (FGM). The rt-CGM systems measure glucose levels continuously and provide automated alarms and alerts at specific glucose levels. Therefore, it is aimed at well-trained patients, capable of making decisions on changing insulin rate, according to recorded glucose levels. On the contrary, glucose levels measured by r-CGM systems are not displayed to the patient in real time, and they can be analyzed in a retrospective manner, by the physician. The Is-CGM or FGM systems measure glucose levels continuously but only display glucose values when the patient scans the sensor [4][14]. The latest FGM device presents alarms for hypoglycemia and hyperglycemia [15].

Some models of CGM require once or twice daily fingersticks with SMBG for calibration, while others can be used without calibration [16].

Whether or not to use the CGM data to make therapeutic decisions depends on the reliability of the device and its MARD (mean absolute relative difference). MARD is used to assess the accuracy of CGM devices. Some of the first commercially available CGMs had a published MARD of >20%. The latest generation of CGM devices has a MARD < 10% [17]. Numerous randomized controlled trials (RCTs) have demonstrated improved glucose control in terms of reduced HbA1c in individuals using CGM compared to those using SMBG [16].

2.2. Emerging and Future Glucose Monitoring Systems

In current clinical practice glucose sensors and insulin infusion cannulas are inserted separately. However, single-port devices are being developed that combine glucose sensing and insulin infusion capabilities on the same platform in order to simplify device insertion and site management [18]. Studies conducted with the goal to evaluate single-port devices performance and its acceptability by patients showed a feasibility of insulin infusion and glucose sensing capabilities in a single device and accurate glucose readings during routine and home use. Moreover, it has been reported that the single-port device was acceptable to most patients and improved satisfaction and convenience [19][20].

In the last few years the progress related to CGM technologies focused on subcutaneous implantable electrochemical glucose sensors in order to optimize biocompatibility and glucose monitoring sensitivity, precision, accuracy, and durability [21].

The development of carbon nanotubes (CNTs) and graphene-based electrodes have been intensively studied, and they demonstrated higher sensitivity and faster response time than traditional electrodes [22].

Moreover, microgel as glucose sensing system has been developed; the peculiarity of this glucose sensor, and what differentiates it from other examples of traditional glucose sensors, is that it provides minimally invasive implantation and a fluorescent signal by transdermal transmission without any external links or electric power sources for CGM [23].

Recently, non-invasive glucose sensing systems have gained significant research interest due to the high sensitivity and better patient compliance, contrary to invasive ones. Major efforts have been devoted to developing entirely non-invasive wearable epidermal glucose sensors toward advanced glycemic control [24].

These emerging sensors can continuously detect glucose in skin interstitial fluid, tears, saliva, and sweat, and include epidermal temporary tattoos, adhesive sensor patches, wrist-worn electrochemically systems, contact lenses, and dental tattoos [25]. Moreover, a new method has been developed to measure the concentration of glucose in hair follicles that accurately reflects the plasma glucose measured by traditional glucose meters [26].

Despite their potential, these technologies are still being studied in order to refine their problems and limitations [24].

References

1. Saeedi, P.; Petersohn, I.; Salpea, P.; Malanda, B.; Karuranga, S.; Unwin, N.; Colagiuri, S.; Guariguata, L.; Motala, A.A.; Ogurtsova, K.; et al. Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: Results from the International Diabetes Federation Diabetes Atlas. Diabetes Res. Clin. Pract. 2019, 157, 107843.

2. Ajjan, R.A. How Can We Realize the Clinical Benefits of Continuous Glucose Monitoring? Diabetes Technol. Ther. 2017, 19, 27–36.

3. Cosentino, F. 2019 ESC Guidelines on Diabetes, Pre-Diabetes and Cardiovascular Diseases developed in collaboration with the EASD. Eur. Heart J. 2020, 41, 255–323.

4. ADA. Diabetes Technology: Standards of Medical Care in Diabetes. Diabetes Care 2020, 43, S77–S88.

5. Battelino, T.; Danne, T.; Bergenstal, R.M.; Amiel, S.A.; Beck, R.; Biester, T.; Bosi, E.; Buckingham, B.A.; Cefalu, W.T.; Close, K.L.; et al. Clinical Targets for Continuous Glucose Monitoring Data Interpretation: Recommendations from the International Consensus on Time in Range. Diabetes Care 2019, 42, 1593–1603.

6. Czupryniak, L.; Barkai, L.; Bolgarska, S.; Bronisz, A.; Broz, J.; Cypryk, K.; Honka, M.; Janez, A.; Krnic, M.; Lalic, N.; et al. Self-monitoring of blood glucose in diabetes: From evidence to clinical reality in Central and Eastern Europe--recommendations from the international Central-Eastern European expert group. Diabetes Technol. Ther. 2014, 16, 460–475.

7. Clarke, S.F.; Foster, J.R. A history of blood glucose meters and their role in self-monitoring of diabetes mellitus. Br. J. Biomed. Sci. 2012, 69, 83–93.

8. Funtanilla, V.D.; Candidate, P.; Caliendo, T.; Hilas, O. Continuous Glucose Monitoring: A Review of Available Systems. Pharm. Ther. 2019, 44, 550–553.

9. Colin, I.M.; Paris, I. Glucose meters with built-in automated bolus calculator: Gadget or real value for insulin-treated diabetic patients? Diabetes Ther. 2013, 4, 1–11.

10. Schmidt, S.; Meldgaard, M.; Serifovski, N.; Storm, C.; Christensen, T.M.; Gade-Rasmussen, B.; Nørgaard, K. Use of an automated bolus calculator in MDI-treated type 1 diabetes: The BolusCal Study, a randomized controlled pilot study. Diabetes Care 2012, 35, 984–990.

11. Rabbone, I.; Scaramuzza, A.E.; Ignaccolo, M.G.; Tinti, D.; Sicignano, S.; Redaelli, F.; De Angelis, L.; Bosetti, A.; Zuccotti, G.V.; Cerutti, F. Carbohydrate counting with an automated bolus calculator helps to improve glycaemic control in children with type 1 diabetes using multiple daily injection therapy: An 18-month observational study. Diabetes Res. Clin. Pract. 2014, 103, 388–394.

12. Doupis, J.; Festas, G.; Tsilivigos, C.; Efthymiou, V.; Kokkinos, A. Smartphone-Based Technology in Diabetes Management. Diabetes Ther. 2020, 11, 607–619.

13. Beck, R.W.; Bergenstal, R.M.; Laffel, L.M.; Pickup, J.C. Advances in technology for management of type 1 diabetes. Lancet 2019, 394, 1265–1273.

14. Bruttomesso, D.; Laviola, L.; Avogaro, A.; Bonora, E.; Del Prato, S.; Frontoni, S.; Orsi, E.; Rabbone, I.; Sesti, G.; Purrello, F. The use of real time continuous glucose monitoring or flash glucose monitoring in the management of diabetes: A consensus view of Italian diabetes experts using the Delphi method. Nutr. Metab. Cardiovasc. Dis. 2019, 29, 421–431.

15. Oyagüez, I.; Merino-Torres, J.F.; Brito, M.; Bellido, V.; Cardona-Hernandez, R.; Gomez-Peralta, F.; Morales-Perez, F. Cost analysis of the flash monitoring system (FreeStyle Libre 2) in adults with type 1 diabetes mellitus. BMJ Open Diabetes. Res. 2020, 8, e001330.

16. Cappon, G.; Vettoretti, M.; Sparacino, G.; Facchinetti, A. Continuous Glucose Monitoring Sensors for Diabetes Management: A Review of Technologies and Applications. Diabetes Metab. J. 2019, 43, 383–397.

17. Martin, C.T.; Criego, A.B.; Carlson, A.L.; Bergenstal, R.M. Advanced Technology in the Management of Diabetes: Which Comes First-Continuous Glucose Monitor or Insulin Pump? Curr. Diab. Rep. 2019, 19, 50.

18. Tauschmann, M.; Hovorka, R. Technology in the management of type 1 diabetes mellitus—Current status and future prospects. Nat. Rev. Endocrinol. 2018, 14, 464–475.

19. Nørgaard, K.; Shin, J.; Welsh, J.B.; Gjessing, H. Performance and acceptability of a combined device for insulin infusion and glucose sensing in the home setting. J. Diabetes Sci. Technol. 2015, 9, 215–220.

20. Tschaikner, M.; Powell, K.; Jungklaus, M.; Fritz, M.; Ellmerer, M.; Hovorka, R.; Lane, S.; Pieber, T.R.; Regittnig, W. Novel Single-Site Device for Conjoined Glucose Sensing and Insulin Infusion: Performance Evaluation in Diabetes Patients During Home-Use. Trans. Biomed. Eng. 2020, 67, 323–332.

21. Chen, C.; Zhao, X.L.; Li, Z.H.; Zhu, Z.G.; Qian, S.H.; Flewitt, A.J. Current and Emerging Technology for Continuous Glucose Monitoring. Sensors 2017, 17, 182.

22. Zhu, Z.G.; Garcia-Gancedo, L.; Flewitt, A.J.; Xie, H.Q.; Moussy, F.; Milne, W.I. A Critical Review of Glucose Biosensors Based on Carbon Nanomaterials: Carbon Nanotubes and Graphene. Sensors 2017, 12, 5996–6022.

23. Zhang, X.J.; Gao, C.M.; Lu, S.Y.; Duan, H.G.; Jing, N.N.; Dong, D.; Shi, C.F.; Liu, M.Z. Anti-photobleaching flower-like microgels as optical nanobiosensors with high selectivity at physiological conditions for continuous glucose monitoring. J. Mater. Chem. B 2014, 2, 5452–5460.

24. Kim, J.; Campbell, A.S.; Wang, J. Wearable non-invasive epidermal glucose sensors: A review. Talanta 2018, 177, 163–170.

25. Gao, W.; Brooks, G.A.; Klonoff, D.C. Wearable physiological systems and technologies for metabolic monitoring. J. Appl. Physiol. 2018, 124, 548–556.

26. Lipani, L.; Dupont, B.; Doungmene, F.; Marken, F.; Tyrrell, R.M.; Guy, R.H.; Ilie, A. Non-invasive, transdermal, path-selective and specific glucose monitoring via a graphene-based platform. Nat. Nanotechnol. 2018, 13, 504–511.