Standardization of continuous glucose monitoring

Over the last years, continuous glucose monitoring (CGM) as an alternative or addition to conventional blood glucose monitoring (BGM) has been gaining more and more importance for patients with diabetes mellitus. Nowadays, CGM and derived therapy parameters such as time in range (TIR) are an integral part of many national and international therapy guidelines [1, 2]. However, unlike for BGM systems, there is no international standard that describes both test procedures and acceptance criteria for CGM systems. This leads to a variety of available CGM systems that differ not only in characteristics like sensor lifetime, application sites and device handling, but also regarding accuracy. Consequently, therapeutic decisions and clinical outcomes, e.g. TIR, may vary depending on the specific CGM system used.

It is well known that there are different factors that have an influence on apparent accuracy assessed in performance studies [3, 4]. These are, for example, the selected study population, distribution of glucose values, frequency of reference measurements, reference measurement procedures and data evaluation. The ultimate goal of CGM performance studies should be to represent a CGM system's accuracy in all situations that occur in daily-life use, including a broad range of glucose values and high rates of change. However, in recent years, study protocols became less and less challenging regarding study procedures. This allowed manufacturers to obtain lower (i.e., better) mean absolute relative difference (MARD) values as the market is getting more and more competitive. In addition, when CGM performance studies are published, comparisons between studies are often limited to accuracy results, like the MARD values, without considering differences in procedures.

Apart from head-to-head studies, where different CGM systems are tested in parallel in the same subjects, only standardized study procedures allow for adequate comparison of different CGM systems. Therefore, in 2019, the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) created a working group on CGM (WG-CGM). The aim of this working group is to develop standards for CGM studies including acceptance criteria and to eventually work with the International Organization for Standardization (ISO) on a guideline.

The first topic which the working group has been working on was the establishment of traceability of glucose values obtained by CGM to materials and methods of higher metrological order [5]. As CGM systems measure glucose in the interstitial fluid, which cannot feasibly be sampled for reference measurements, there is a break in the traceability chain. This break has to be adequately addressed by manufacturers.

Currently, WG-CGM establishes suitable and scientifically sound study and analytical procedures to test CGM accuracy. So far, procedures to improve reference measurements were developed [6] as well as a method to statistically evaluate and display CGM accuracy [7]. This work was supported by the IfDT in cooperation with the Diabetes Center Berne in Switzerland based on long-standing experience and additional research activities. The definition of detailed study design and procedures including the study population, requirements for inductions of glucose excursions, definition of suitable reference measurements etc. is the next step. The aim is to provide standardized procedures that ensure representative and reproducible testing of all relevant aspects to improve consistency and transparency in CGM accuracy reporting.

If we use CGM derived parameters for therapy assessment it is important to have accurate CGM systems without relevant bias.

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References

1. **American Diabetes Association.** Standards of Medical Care in Diabetes. *Diabet. Care,* 2022, 45(Suppl 1). [link]
2. **Holt, R. I. G., DeVries, J. H., Hess-Fischl, A., Hirsch, I. B., Kirkman, M. S., Klupa, T. et al.** The management of type 1 diabetes in adults. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetologia*, 2021, 64(12), s. 2609-2652. [link]
3. **Reiterer, F., Polterauer, P., Schoemaker, M., Schmelzeisen-Redecker, G., Freckmann, G., Heinemann, L. et al.** Significance and Reliability of MARD for the Accuracy of CGM Systems. *J Diabet. Sci. Technol.,* 2017, 11(1), s. 59-67. [link]
4. **Heinemann, L., Schoemaker, M., Schmelzeisen-Redecker, G., Hinzmann, R., Kassab, A., Freckmann, G. et al.** Benefits and Limitations of MARD as a Performance Parameter for Continuous Glucose Monitoring in the Interstitial Space. *J Diabet. Sci. Technol.,* 2020, 14(1), s. 135-50. [link]
5. **Freckmann, G., Nichols, J. H., Hinzmann, R., Klonoff, D. C., Ju, Y., Diem, P. et al.** Standardization process of continuous glucose monitoring: Traceability and performance. *Clin. chim. acta; Int. J. Clin. Chem.,* 2021, 515, s. 5-12. [link]

6. **Pleus, S., Eichenlaub, M., Gerber, T., Eriksson Boija, E., Makris, K., Haug, C. et al.** Improving the Bias of Comparator Methods in Analytical Performance Assessments Through Recalibration. *J Diabet. Sci. Technol.*, 2022, 19322968221133107. **[link]**
7. **Eichenlaub, M., Stephan, P., Waldenmaier, D., Pleus, S., Rothenbühler, M., Haug, C. et al.** Continuous Glucose Deviation Interval and Variability Analysis (CG-DIVA): A Novel Approach for the Statistical Accuracy Assessment of Continuous Glucose Monitoring Systems. *J Diabet. Sci. Technol.*, 2022, 19322968221134639. **[link]**