Application of medium-term metrics for assessing glucose homeostasis: usefulness, strengths and weaknesses

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Running title: Medium-term metrics and dysglycaemia

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Key words: Medium-term metrics, glucose homeostasis, continuous glucose monitoring

Word count : 3185

ABSTRACT

This review is aimed at addressing the issue as to whether or not the newer metrics developed for continuous glucose monitoring (real-time or intermittently scanned CGM) enhance the assessment of the "glucose tetrad": ambient hyperglycaemia, short-term glycaemic variability, postprandial glucose excursions and hypoglycaemia. The ever increasing number of metrics offered with real-time CGM (rtCGM) or intermittently scanned CGM (isCGM) includes intermediate-term indicators referred to as the "Time- in Ranges", i.e. the time in range 70-180 mg/dL (TIR 70-180), the time above range > 180 mg/dL (TAR) and the time below range of < 70 or 54 mg/dL (TBR < 70 or TBR < 54 mg/dL). The two former are highly correlated with HbA1c levels and can therefore serve as short or medium- term markers of the ambient hyperglycaemia according to whether glucose sensors are worn over periods of several days or weeks. The two latter indices (the TBR < 70 or < 54) are more relevant for capturing hypoglycaemic events and quantifying their magnitude and duration in contrast to the random spot testing with self-blood glucose monitoring. Although the analysis of 24-h glucose profiles by CGM provides a very valuable method for quantifying postprandial glucose excursions and short-term glycaemic variability neither can be fully represented by the TIR metrics, needed for a more comprehensive assessment of glucose homeostasis.

Introduction

From a glucocentric view point, there is increasing evidence that the management of dysglycaemia associated with diabetes, either type 1 or 2, should target the four main components of the "glucose tetrad": sustained chronic hyperglycaemia, glycaemic variability, excessive postprandial glucose excursions and hypoglycaemic episodes [1-6], all of whom are associated with or responsible for diabetes complications [2, 7-13]. The objectives of any therapeutic approach are to maintain all these components within selected thresholds that should be personalized [6]. In a person with a short duration of the disease, long life expectancy, high motivation and without any evidence of comorbidities or vascular complications, tight glycaemic control is usually recommended [6], i.e. a HbA1c level < 7% (53 mmol/mol), coefficient of variation for glucose (%CV) ≤ 36%, 2-h postprandial glucose concentration < 180 mg/dL (10.0 mmol/L) and random glucose levels > 70 mg/dL (3.9 mmol/L) in order to avoid the consequence of hyperglycaemia and/or hypoglycaemic (figure 1). However, less stringent targets may be considered for more vulnerable persons in whom severe hypoglycaemia can be associated with or responsible for harmful effects [6]. The last decade has been marked by the development of new systems of continuous glucose monitoring (CGM) that can be worn over extended periods of time (several consecutive days) that provide real-time (rtCGM) or frequent intermittently scanned (isCGM) glucose readings [14,15]. The utilization of such technologies has therefore raised the question whether additional metrics could better represent glucose homeostasis to further bridge the gap between the long-term HbA1c testing [16] and the short-term indices of dysglycaemia such as the 24-h mean daily glucose concentration and the within or between-day glucose variability [17,18]. In addition, CGM devices have the capability to capture the trends towards hyper or hypoglycaemia thus offering the opportunity to intervene before the occurrence of symptomatic episodes. These benefits are denied when relying on random self-monitoring of blood glucose. With the introduction of CGM newer metrics were introduced which include the percentages of time spent in or out-of target ranges [14,19,20] and glucose management indicators (GMI) [21]. The present review is aimed at exploring the usefulness and potential limitations of these medium-term metrics of glucose homeostasis.

Definitions and thresholds

Time in "Ranges"

The percent of time within and outside established glycaemic targets are represented by a cluster of metrics divided into 3 categories based on the time spent within, below and above the range of the glycaemic thresholds and referred to as TIR, TBR and TAR [19,20]. This relatively new way for standardizing CGM metrics is particularly useful for clinical care and well accepted by healthcare professionals [22]. The recognised normal glucose range in individuals without diabetes is between 70 and 140 mg/dL (3.9 and 7.8 mmol/L) [19]. The lower limit of 70 mg/dL (3.9 mmol/L) corresponds to the definition of hypoglycaemia [23,24] and the threshold for activation of counter-regulatory hormones [25]. The upper limit of 140 mg/dL (7.8 mmol/L) is the value used to diagnosis impaired glucose tolerance at two hours during a 75-g oral glucose tolerance test (OGTT) [26]. In addition, during the real life of persons without any glucose dysregulation this cut point value is rarely enforced even during post meal periods [27]. However, it has been widely acknowledged that this value of 140 mg/dL (7.8 mmol/L) is low when applied to populations with diabetes and therefore 180 mg/dL (10.0 mmol/L) or even 250 mg/dL (13.9 mmol/L) have been recommended [6,14,20]. This proposition is obvious in clinical practice as many patients with type 1 diabetes, even those exhibiting a glycaemic control considered to be “satisfactory”, spend a major part of their time above 140 mg/dL (7.8 mmol/L) [19,28,29,30], in part due to their fear of hypoglycaemia. In type 2 diabetes, the glycaemic threshold of 140 mg/dL (7.8mmol/L) is reasonable in well-controlled patients, i.e. in those who maintain their HbA1c levels between 5.7 and 6.5% (39 and 48 mmol/mol) [31,32]. However as soon as the HbA1c levels rise above this range, analysis of 24-h glycaemic profiles demonstrate that the duration of time spent above 140 mg/dL (7.8 mmol/L) and 180 mg/dL (10.0 mml/L) steadily increased especially after breakfast during the period of the extended dawn phenomenon [33,34]. Therefore the consensus is that a broader range of glucose fluctuations be adopted in persons with diabetes. Consequently, 180 mg/dL (10.0 mmol/L) appears as the best compromise in real life situation for people with diabetes [22]. Even though 70 and 180 mg/dL (3.9 and 10.0 mmol/L) are considered to be the most appropriate thresholds for visualizing the TIR, TBR and TAR, other CGM glycaemic ranges have also been proposed [14,20], e.g. the lower glucose level can be < 54 mg/dL (3.0 mmol/L), corresponding to the period of established hypoglycaemia with the presence of neuroglycopenic symptoms [25].

Also when considering hyperglycaemia above 180 mg/dL (10.0 mol/L) it can be subdivided into 2 levels according to whether the glucose values remain between 180 (10.0 mmol/L) and 250 mg/dL (13.9mmol/L) (level 1) or above 250 mg/dL (13.9mmol/L) (level 2). Dividing the hypoglycaemic and hyperglycaemic ranges into 2 additional levels has the advantage of highlighting the level of urgency required to address the glucose disorder. The advantage of the rtCGM is its ability to demonstrate time related trends in blood glucose levels to allow the individual to intervene in order to avoid hypo-

or hyperglycaemia . A group of experts have recently reached a consensus on the times spent in "Ranges" [6,14,20]. In a general population of persons with type 1 or type 2 diabetes it is recommended that the percentage of time spent within the range of 70 (3.9mmol/L) to 180 mg/dL (10.0mmol/L) (TIR) should be greater than 70% with less than 4% and 1% of time below range (TBR) according to whether the thresholds is 70 or 54 mg/dL (3.9 or 3.0 mmol/L), respectively. For the time above range (TAR), less than 25% and 5% of time have been selected based on a threshold of 180 or 250 mg/dL (10.0 or 13.9 mmol/L), respectively. These CGM-based targets and recommendations should be adjusted to the patient's characteristics: less stringent in elderly people and more stringent in gestational diabetes and during pregnancy in people with diabetes [19].

Glucose management indicator

In their search to find new metrics for medium-term assessment of glucose homeostasis, diabetologists use CGM to provide an estimate of the glucose exposure by averaging the 24-h mean daily glucose concentration over a preselected time interval of at least 10-14 days [14]. The A1c-Derived Average Glucose (ADAG) Study Group [35] found an excellent correlation (r^2= 0.92, p < 0.0001) between laboratory-measured HbA1c and the average mean glucose concentration displayed by CGM devices worn over several days (figure 2) [35] permitting the estimation of the mean glucose levels from pre-specified HbA1c levels. A laboratory-measured HbA1c of 6% (42 mmol/mol) corresponds to an average mean glucose concentration of 126 mg/dL (7.0 mmol/L) and any 1% increment of HbA1c can be converted to a 29 mg/dL (1.61 mmol/L) increase in the mean glucose concentration [35]. This relationship can also be made in the reverse direction, i.e. from the mean glucose concentration to the HbA1c levels, thus introducing the terminology of estimated HbA1c (eHbA1c) [36]. By using modern devices, Beck et al [36] validated a formula that describes this relationship: eHbA1c (%) = 3.38 + 0.02345 x [mean glucose expressed as mg/dL]. More recently, this equation has been slightly revised and replaced by a new one permitting to compute an additional metrics referred to as the glucose management indicator (GMI): GMI (%) = 3.31 + 0.02392 x [mean glucose expressed as mg/dL] (figure 2) [21]. It should be remembered however that the HbA1c level measured in a laboratory at a given time point of blood sampling integrates the overall chronic glucose exposure, i.e. the ambient hyperglycemia, over the 3-month period that precedes the laboratory determination [21] in contrast to the CGM derived eHbA1c and GMI based on the glucose exposure during the period of CGM.

Taking an example of a patient who visits his (her) physician just after having worn a glucose sensor for 14 days, several situations can be encountered. Firstly, the value of the GMI can be lower than

that of the laboratory HbA1c. This situation is mostly observed when the patient's compliance to therapy (dietary measures, exercise and/or pharmacological treatments) is better during the few days of CGM compared with the rest of the time. Secondly, and in contrast, the calculation of the GMI can result in higher values than those given by the laboratory for HbA1c levels. This can occur when the out-of CGM monitoring periods involve frequent hypoglycaemic events. Thirdly, the final situation, which is fortunately the most frequent, corresponds to patients in whom the two values are closely related. This implies that the overall glucose homeostasis has been stable over some time. The two first aforementioned situations with discordant GMI and laboratory HbA1c values can be misinterpreted and disturbing for patients and healthcare professionals alike, especially if the terms "eHbA1c" and "HbA1c" are both used. However, if differences do occur, provided the reasons are well understood, this can motivate the patient to improve his (her) adherence to treatment long-term and not be limited to only the few weeks preceding clinic visits whilst also allowing more realistic HbA1C targets to be defined [21].

Relationships of medium versus long-and short-term metrics

Prior to reporting the relationships between the different categories of metrics, it should be noted that even though at first glance, the time in "Ranges" and GMI can be considered medium term-indicators of glucose homeostasis, it remains difficult to define the frontier between medium and long-term metrics. When, for instance the time in "Ranges" are derived from rtCGM or isCGM worn for periods of several weeks or months long-term, GMI becomes a long-term marker of overall glucose exposure [37].

Relationship between HbA1c and mean glucose concentrations

The existence of positive strong relationships between HbA1c and mean glucose concentrations has been described in the preceding paragraph, however the observation of differences between trials needs to be explained [21,35,36,38]. Both the eHbA1c and GMI reflect the mean glucose concentration computed from the plot of CGM-measured mean glucose concentrations, which are linearly related to the laboratory HbA1c. However, the slope of the relationship will depend upon the duration of insertion of the CGM device, the longer the duration the better the accuracy, and also on the type of glucose sensor used. It is commonly acknowledged that the results using the most modern CGM devices are more reliable than those provided by older versions. Consequently, the latest formula (GMI=3.31 + 0.02392 x [mean glucose concentration]) established with the Dexcom G4 and G5 sensors [21] (figure 2) and based on the data of Beck [36] and Heinemann (the HypoDE study) [38] is now the reference standard that should be adopted, substituting the previous ADAG equation

calculated using earlier technologies (CGMS, Medtronic, Minimed) [35]. The small differences between the two slopes are illustrated in figure 2.

Relationships between HbA1c or mean glucose concentration and TIR 70-180 or TAR >180

Utilizing data from of 4 randomised controlled trials [38-41] conducted in a 545 adults with type 1 diabetes, Beck et al [42] calculated the correlation between CGM metrics and laboratory-measured HbA1c by using the Spearman partial correlation coefficients. The main results can be summarized as follows: (i) Negative correlations (r = - 0.73 and – 0.92) were observed when TIR70-180 were tested against HbA1c and mean glucose concentrations, respectively; (ii) Positive correlations (r = + 0.77 and + 0.98) were found when TAR > 180 were plotted against HbA1c levels and mean glucose concentrations, respectively. These findings demonstrate that the CGM measures such as the TIR70-180 or TAR > 180 are highly correlated with the mean glucose concentration and less strongly with HbA1c levels. In a population of 247 persons, 100 with type 1 diabetes and 147 with type 2 diabetes we found a strong negative correlation ($r = - 0.85$, $p < 0.001$) between the TIR70-180 and mean glucose concentration which are in agreement with those of Beck et al [42]. However, the meaning of this seemingly high correlation remains questionable when it comes to be extrapolated into clinical practice. As shown in figure 3, the limits of the 95% confidence interval around the fitted linear regression line between the TIR70-180 and the mean glucose concentration range from 110 to 190 mg/dL (6.1 to 10.5 mmol/L) for a mean glucose of 150 mg/dL (8.3 mmol/L) which corresponds to 70 per cent of the time spent between 70 and 180 mg/dL (3.9 and 10.0 mml/L), i.e. the lower percentage recommended by the International consensus [20]. Reverting to the correlation between the TIR70-180 and HbA1c, it should be noted that the mean corresponding values of the TIR-70-180 and HbA1c levels differ between studies [42], although by plotting these two values reported in 18 articles, an excellent linear regression was observed: r = - 0.84 (figure 4) [43]. The analysis of the slope showed that a TIR70-180 of 70% corresponds to an HbA1c level of 6.7% (50 mmol/mol) and that any 10% change in TIR70-180 (e.g. between 50 and 60%) is equivalent to a 0.8% (9 mmol/mol) change in HbA1c. This enthusiasm toward these equivalences should be attenuated by the fact the confidence interval of the 0.8% change in HbA1C ranges between – 0.95 and 1.21%.

Bringing all these studies together strongly suggest that an overall comprehensive appraisal of the ambient hyperglycaemia cannot be restricted to the determination of one single metrics, but should include not only the assessment of laboratory-measured HbA1c levels, considered to be the gold standard [16], but also the TIR70-180 [20] and the GMI [21], based on the average 24-h mean daily

glucose concentrations over several days. Consequently, it appears that the CGMs and more specifically the rtCGM and isCGM play a key role to satisfy this requirement [14,15,37].

Relationships between glucose variability, hypoglycaemia and TIR 70-180 or TBR < 70

Despite no compelling evidence that rapid glucose fluctuations from peaks to nadirs, also referred to as within-and between-day glucose variability [11,17,44,45] are a risk factor for long-term diabetes complications, several observational studies have reported an association between these indices of dysglycaemia and biomarkers of activation of oxidative stress [46,47,48], one of the key players in the pathophysiology of diabetes cardiovascular outcomes [49] There is however increasing evidence that the frequency of hypoglycaemia increases exponentially with increasing short-term glycaemic variability, which progressively increases from type 2 diabetes treated with oral agents such as sulfonylureas to type 1 diabetes with an intermediary stage represented by insulin -treated type 2 diabetic patients [17]. More recently it has been demonstrated that short-term glucose variability (coefficient of variation, %CV) is a major contributor to and predictor of level 2 hypoglycaemia (glucose value < 54 mg/dL, i.e. < 3.0 mmol/L) in type 1 diabetes [5]. As the TBR < 70 is the best metrics for quantifying the presence of hypoglycaemia (both levels 1 and 2), we tested whether short-term glucose variability can be deduced from the TBR < 70 mg/dL (3.9 mmol/L). In a population of 247 persons with type 1 and type 2 diabetes, the TBR < 70 was positively and significantly correlated with the %CV: $r = 0.67$ ($p < 0.001$) (figure 5). For a 4% TBR threshold [20], the corresponding value of the glucose variability was 33% (95%CI = 18 to 48%). However, the seemingly good correlation between the %CV and the TBR < 70 is in fact highly questionable because persons exhibiting a mean glucose variability of 33% can have either a stable or labile diabetes according to whether their real %CV is closer to the lower (18%) or upper value (48%) of the 95% confidence interval, respectively. It can therefore be concluded that the TBR is unable to estimate the short-term glycaemic variability which requires specific metrics among whom [45] the %CV appears to be the most applicable for clinical practice [17,18] with a threshold of 36% to separate stable from labile diabetes. However daily repeated measures of short-term glucose variability can provide an estimate of longer-term variation of glucose homeostasis if averaged over several days. It should be mentioned that the “averaged daily CV”, calculated by using the abovementioned computation, should not be confused with the “daily CV by average”, which is provided by averaged glucose profiles over time. The latter, which is usually smaller than the former [50], underestimates the glycaemic variability, the underestimation becoming more and more marked with worsening synchrony of glucose patterns from day-to-day [51]. Therefore a large disparity between the

“averaged daily CV” and the “daily CV by average” reflects high between-day glucose variability. Finally, it is necessary not to confuse the short or medium- term variability and the long-term variability of glucose homeostasis (visit-to-visit variability), which is usually calculated by the standard deviation (SD) and CV of fasting blood glucose or HbA1c measured from monthly or quarterly spot blood sampling [52,53,54].

Conclusion: from the “glucose tetrad” to an extended group of metrics

It appears that a broad range of metrics representing short, medium and long-term glycaemia is necessary to quantify or detect the four main components of dysglycaemia (figure 1). As some of these metrics are more or less inter-correlated, they could, at first glance, appear to be somewhat redundant, but our present review implies that the word complementarity is more appropriate. The assessment of ambient hyperglycaemia (figure 6) should not be limited to quarterly measurements of HbA1c, but should encompass medium -term metrics such as those of the TIR, TAR and GMI [14,20-22] that integrate the chronic glucose exposure overall several days or weeks. The detection of hypoglycaemia, which is limited when patients are relying on spot capillary glucose testing, can be enhanced using the TBR < 70 or < 54 mg/dL over short-or medium -term periods of time. Whereas the glycaemic variability based on daily glucose fluctuations is normally the remit of short-term metrics, the use of CGM devices over longer periods of time permits a broader assessment of this parameter. However, when such medium-term measurements are performed, our recommendation would be to express the results as “averaged glycaemic variability” rather than as “glycaemic variability by average”. In other words, the daily measure of glycaemic variability (%CV) should be averaged over several consecutive days, because the use of the “glycaemic variability by average” leads usually to an underassessment of glucose fluctuations. Finally, the postprandial glucose excursions contribute both to the chronic glucose exposure and glycaemic variability and its assessment requires specific determinations [17]. According to the data provided by studies of 24-h glycaemic profiles in people with type 2 diabetes [31-33], postprandial glucose peaks usually occur 60 to 90 minutes from the beginning of the meal and therefore special attention should be given to the the 1-hour glucose value that appears to be the most appropriate for testing postprandial glucose excursions [55-57].

Currently and as represented in figure 6, the target ranges and thresholds have been defined for all the aforementioned parameters, ambient hyperglycaemia, glycaemic variability, hypoglycaemia and postprandial glucose [6,20], with most of them requiring the use of CGM technologies and more specifically of those also permitting medium- and long-term recording [58].

Disclosure of interest

The authors declare that they have no competing interest and that no funding has been provided for this work

Acknowledgements

The authors wish to thank professor Nicolas Molinari (University of Montpellier) for his assistance in the analysis of statistical data

References

[1] Monnier L, Colette C, Owens DR. Integrating glycaemic variability in the glycaemic disorders of type 2 diabetes: a move towards a unified glucose tetrad concept. Diabetes Metab Res Rev 2009;25:393-402

[2] Monnier L, Colette C, Schlienger J-L, Bauduceau B, Owens DR. Glucocentric risk factors for macrovascular complications in diabetes : glucose « legacy » and « variability »- what we see, know and try to comprehend. Diabetes Metab 2019;45:401-408

[3] Murata GH, Hoffman RM, Shah JH, Wendel CS, Duckworth WC. A probabilistic model for predicting hypoglycemia in type 2 diabetes mellitus. The diabetes outcomes in veterans study (DOVES) Arch Int Med 2004;164:1445-1450

[4] Cryer PE. Glycemic goals in diabetes: trade-off between glycemic control and iatrogenic hypoglycemia. Diabetes 2014;63:2188-2195

[5] Monnier L, Wojtusciszyn A, Molinari N, Colette C, Renard E, Owens D. Respective contributions of glycemic variability and mean glucose as predictors of hypoglycemia in type 1 diabetes: are they equivalent? Diabetes Care 2020;43:821-827

[6] American Diabetes Association. Glycemic targets: standards of medical care in diabetes-2020. Diabetes Care 2020;43 (Suppl 1): S66-S76

[7] The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 1993;329:977-986

[8] The Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) Study Research group. Intensive diabetes treatment and cardiovascular outcomes in type 1 diabetes. The DCCT/EDIC Study 30 year follow-up. Diabetes Care 2016;39:686-693

[9] Bebu I, Schade D, Braffett B, Kosiborod M, Lopes-Virella M, Soliman EZ, et al., on behalf of the DCCT/EDIC Research Group. Risk factors for first and subsequent CVD events in type 1 diabetes: The DCCT/EDIC Study. Diabetes Care 2020;43:867-874

[10] Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HAW. 10-year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med 2008;359:1577-1589

[11] Ceriello A, Monnier L, Owens D. Glycaemic variability in diabetes: clinical and therapeutic implications. Lancet Diabetes Endocrinol 2019;7:221-230

[12] Zoungas S, Patel A, Chalmers J, de Galan BE, Li Q, Biostat M, et al., for the ADVANCE Collaborative Group. Severe hypoglycemia and risk of vascular events and death. N Engl J Med 2010;363:1410-1418

[13] Davis SN, Duckworth W, Emanuele N, Hayward RA, Wiitala WL, Thottapurathu L et al, Investigators of the Veterans Affairs Diabetes Trial. Effects of severe hypoglycemia on cardiovascular outcomes and death in the Veterans Affairs Diabetes Trial. Diabetes Care 2019;42:157-163

[14] Danne T, Nimri R, Battelino T, Bergenstal RM, Close KL, DeVries JH, et al. International consensus on use of continuous glucose monitoring. Diabetes Care 2017;40:1631-1640

[15] American Diabetes Association. Diabetes Technology: standards of medical care in diabetes-2020. Diabetes Care 2020 (Suppl 1): S77-S88

[16] Sacks DB. Measurement of HbA1c. A new twist in the path to harmony. Diabetes Care 2012;35:2674-2680

[17] Monnier L, Colette C, Owens DR. The application of simple metrics in the assessment of glycemic variability. Diabetes Metab 2018;44:313-319

[18] Monnier L, Colette C, Wojtusciszyn A, Dejager S, Renard E, Molinari N, et al. Toward defining the threshold between low and high glucose variability in diabetes. Diabetes Care 2017;40:832-838

[19] Agiotratidou G, Anhalt H, Ball D, Blonde L, Gourgari E, Harriman KN, et al. Standardized clinically meaningful outcome measures beyond HbA1c for type 1 diabetes: A consensus report of the American Association of clinical Endocrinologists, the American Association of Diabetes Educators, the American Diabetes Association, the Endocrine Society, IDRF International, the Leona M and Harry B Helmsley Charitable Trust, the Pediatric Endocrine Society and the T1D Exchange. Diabetes Care 2017;40:1622-1630

[20] Battelino RM, Danne T, Bergenstal RM, Amiel SA, Beck R, Biester T, 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

[21] Bergenstal RM, Beck RW, Close KL, Grunberger G, Sacks DB, Kowalski A, et al. Glucose management indicator (GMI): A new term for estimating A1c from continuous glucose monitoring. Diabetes Care 2018;41:2275-2280

[22] Advani A. Positioning time in range in diabetes management. Diabetologia 2020;63:242-252

[23] Workgroup on hypoglycemia. American Diabetes Association. Defining and reporting hypoglycemia in diabetes: a report from the American Diabetes Association Workgroup on hypoglycemia. Diabetes Care 2005;28:1245-1249

[24] The International Hypoglycaemia Study Group. Glucose concentrations of less than 3.0 mmol/L (54 mg/dL) should be reported in clinical trials: a joint position statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 2017;40:155-157

[25] Cryer PE. The prevention and correction of hypoglycemia. In Handbook of Physiology, Section 7, volume II, The Endocrine Pancreas and Regulation of Metabolism. Jefferson LS, Cherrington AD, Eds New York, Oxford University Press, 2001,p1057-1092

[26] American Diabetes Association. Classification and diagnosis of diabetes: standards of medical care indiabetes-2020. Diabetes Care 2020;43 (Suppl 1): S14-S31

[27] Rhee MK, Ho YL, Raghavan S, Vassy JL, Cho K, Gagnon D, et al. Random plasma glucose predicts the diagnosis of diabetes. Plos One 2019;14:e0219964

[28] Tamborlane WV, Beck RW, Bode BW, Buckingham B, Chase HP, Clemons R, et al. The Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group. Continuous glucose monitoring and intensive treatment of type 1 diabetes. N Engl J Med 2008;359:1464-1476

[29] Soupal J, Petruzelková L, Flekac M, Pelcl T, Matoulek M, Danková M, et al. Comparison of different treatment modalities for type 1 diabetes, including sensor-augmented insulin regimens in 52 weeks of follow-up: a COMISAIR study. Diabetes Technol Ther 2016;18:532-538

[30] Soupal J, Petruzelková L, Grunberger G, Hásková A, Flekac M, Matoulek M. Glycemic outcomes in adults with T1D are impacted more by continuous glucose monitoring than by insulin delivery method: 3 years of follow-up from the COMISAIR Study. Diabetes Care 2020;43:37-43

[31] Monnier L, Colette C, Dejager S, Owens DR. Mild « dysglycemia » in type 2 diabetes : to be neglected or not. J Diabetes and its Complications 2015;104:370-375

[32] Monnier L, Colette C, Dejager S, Owens D. Residual dysglycemia when at target of 7% (53 mmol/mol) in persons with type 2 diabetes. Diabetes Res Clin Pract 2014;140:370-375

[33] Monnier L, Colette C, Dunseath G, Owens DR. The loss of postprandial glycemic control precedes stepwise deterioration of fasting with worsening diabetes. Diabetes Care 2007;30:263-269

[34] Monnier L, Colette C, Dejager S, Owens D. Magnitude of the dawn phenomenon and its impact on the overall glucose exposure in type 2 diabetes. Is this of concern? Diabetes Care 2013;36:4057-4062

[35] Nathan DM, Kuenen J, Berg R, Zheng H, Schoenfeld D, Heine RJ, for the A1c-Derived Average Glucose (ADAG) Study Group. Translating the A1c assay into estimated average glucose value. Diabetes Care 2008;31:1473-1478

[36] Beck RW, Connor CG, Mullen DM, Wesley DM, Bergenstal RM. The fallacy of average: how using HbA1c alone to assess glycemic control can be misleading. Diabetes Care 2017;40:994-999

[37] Edelman SV, Argento NB, Pettus J, Hirsch IB. Clinical implications of real-time and intermittently scanned continuous glucose monitoring. Diabetes Care 2018;41:2265-2274

[38] Heinemann L, Freckmann G, Ehrmann D, Faber-Heinemann G, Guerra S, Waldenmaier D, et al. Real time continuous glucose monitoring in adults with type 1 diabetes and impaired hypoglycaemia awareness or severe hypoglycaemia treated with multiple daily insulin injections (HypoDE): a multicenter, randomised controlled trial. Lancet 2018;391:1367-1377

[39] The Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group. The effect of continuous glucose monitoring in well-controlled type 1 diabetes. Diabetes Care 2009;32:1378-1383

[40] Aleppo G, Ruedy KJ, Riddleworth TD, Kruger DF, Peters AL, Hirsch I, et al., for the REPLACE-BG group. REPLACE-BG: A randomized trial comparing continuous glucose monitoring with and without routine blood glucose monitoring in adults with well-controlled type 1 diabetes. Diabetes Care 2017;40:538-545

[41] Beck RW, Riddleworth T, Ruedy K, Ahmann A, Bergenstal R, Haller S, et al., for the DIAMOND Study Group. Effect of continuous glucose monitoring on glycemic control in adults with type 1 diabetes using insulin injections: the DIAMOND randomized clinical trial. JAMA 2017;317:371-378

[42] Beck RW, Bergenstal RM, Cheng P, Kollman C, Carlson AL, Johnson ML ,et al. The relationships between time in range, hyperglycemia metrics, and HbA1c. J Diabetes Sci Technol 2019;13:614-626

[43] Vigersky RA, Mc Mahon C. The relationship of hemoglobin A1c to time-in-range in patients with diabetes. Diabetes Technol Ther 2019;21:81-85

[44] Rodbard D. Glucose variability: a review of clinical applications and research development. Diabetes Technol Ther 2018;20(suppl 2):S2-5-S2-15

[45] Kovatchev BP. Metrics for glycaemic control-from HbA1c to continuous glucose monitoring. Nat Rev Endocr 2017;13:425-436

[46] Monnier L, Mas E, Ginet C, Michel F, Villon L, Cristol J-P, et al. Activation of oxidative stress by acute glucose fluctuations, compared with sustained chronic hyperglycemia in patients with diabetes. JAMA 2006;295:1681-1687

[47] Ceriello A, Esposito K, Piconi MA, Ihnat MA, Thorpe JE, Testa R, et al. Oscillating glucose is more deleterious to endothelial function and oxidative stress than mean glucose in normal and type 2 diabetic patients. Diabetes 2008;57:1349-1354

[48] Hirsch IB. Glycemic variability and diabetes complications: does it matter? Of course it does! Diabetes Care 2015;38:1610-1614

[49] Brownlee M. The pathophysiology of diabetic complications: a unifying mechanism. Diabetes 2005;54:1615-1625

[50] Bajaj HS, Venn K, Ye C, Patrick A, Kalra S, Khandwala H, et al. Lowest glucose variability and hypoglycemia are observed with the combination of a GLP-1 receptor agonist and basal insulin (VARIATION Study). Diabetes Care 2017;40:194-200

[51] Rodbard D. Interpretation of glucose monitoring data: glycemic variability and quality of glycemic control. Diabetes Technol Ther 2000;11 (suppl 1): S-55-S-61

[52] Gorst C, Kwok CS, Adam S, Buchan I, Kontapantelis E, Myint PK, et al. Long-term glycemic variability and risk of adverse outcomes: a systemic review and meta-analysis. Diabetes Care 2015;38:2354-2369

[53] Critchley JA, Carey IM, Harris T, DeWilde S, Cook DG. Variability in glycated hemoglobin and risk of poor outcomes among people with type 2 diabetes in a large primary care cohort study. Diabetes Care 2019;42:2237-2246

[54] Sheng C-S, Tian J, Miao Y, Cheng Y, Yang Y, Reaven PD, et al. Prognostic significance of long-termHbA1Cvariability for all-cause mortality in the ACCORD trial. Diabetes Care 2020 Mar; dc192589.http://doi.org/10.2337/dc19-2589

[55] Ceriello A. Targeting one-hour post meal glucose: is it time for a paradigm switch in diabetes management? Diabetes Technol Ther 2017;19:493-497

[56] International Diabetes Federation. Guideline Development Group. Guideline for management of post-meal glucose in diabetes. Diabetes Res Clin Pract 2014; 103: 256-268

[57] Bergman M, Abdul-Ghani M, DeFronzo RA, Manco M, Sesti G, FiorentinoTV, et al. Review of methods for detecting glycemic disorders. Diabetes Res Clin Pract 2020, online June 1. https://doi.org/10.1016/j.diabres.2020.108233

[58] Malorino MI, Signoriello S, Maio A, Chiodini P, Bellastella G, Scappaliccio L, et al. Effects of continuous glucose monitoring on metrics of glycemic control in diabetes: a systematic review with meta-analysis of randomized controlled trials. Diabetes Care 2020;43:1146-1156

Legends of figures

Figure 1: Assessment of glucose homeostasis from the « glucose tetrad » with recommended target ranges and thresholds. %CV: coefficient of variation for glucose; PPG: postprandial glucose

Figure 2: Regression lines used for computing the eHbA1c (estimated HbA1c) and the GMI (Glucose Management Indicator) on the Y axis from the CGM-measured mean glucose concentration on the X axis. The assessments of eHbA1c and GMI are based on the results of the ADAG study [35] and on data sets combining the Beck [36] and HypoDE [38] equations. Slight differences are observed between the 2 regression lines at least when CGM-measured mean glucose concentrations remain within a range from 100 (5.6mmol/L) to 200 mg/dL (11.1 mmol/L)(shaded area)

Figure 3: Relationship of the TIR (X axis expressed as percentage from 0 to 100) versus the mean glucose concentration (Y axis expressed as mg/dL or mmol/L) in 247 patients with either type 1 or type 2 diabetes. The limits of the 95% confidence band (shaded areas) for the measured mean glucose values around the fitted line are indicated as broken lines. The lower thresholds of the 70% TIR recommended by the International Consensus corresponds to a mean glucose concentration of 150 mg/dL (8.3 mmol/L) [95%CI = 110-190 mg/dL (6.1-10.5 mmol/L)

Figure 4: Relationship between HbA1C (%) and Time-in Range (%). The 18 points correspond to the mean paired HbA1c and TIR data sets reported in different articles. A TIR value of 70% corresponds to an HbA1c level of 6.7% (50 mmol/mol) and any 10% change in TIR (e.g. from 50 to 60%) is equivalent to a 0.8% (9mmol/mol) change in HbA1c [adapted from reference 43]

Figure 5: Relationship of the TBR expressed as percentage after transformation into its square root (X axis, √TBR) versus the coefficient of variation for glucose (%CV, Y axis expressed as percentage). The square roots were used according to the analysis of the residuals in order to improve the linear fitting of the relationship. The broken lines indicate the limits of the 95% confidence band (shaded area) for the %CV around the fitted line. The threshold of the 4% TBR (i.e.√4% = 2 on the X axis) recommended by the international consensus corresponds to a %CV of 33% (95% CI = 18-48%)

Figure 6: Assessment of the glucose homeostasis from the most recently extended group of metrics that include long-, intermediate-and short-term metrics.
TIR: Time in Range between 70 and 180 mg/dL (3.9 and 10.0 mmol/L) ; TAR: Time above Range >180 mg/dL (10.0 mmol/L) ; TBR: Time below Range < 70 or 54 mg/dL (3.9 or 3.0 mmol/L) ; GMI: Glucose

Management Indicator derived from the measured mean glucose concentration; %CV: coefficient of variation for glucose; PPG : Postprandial glucose