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Glycaemia dynamics in gestational diabetes mellitus

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ABSTRACT

Pregnant women may develop gestational diabetes mellitus (GDM), a disease of pregnancy characterised by maternal and fetal hyperglycaemia with hazardous consequences to the mother, the fetus, and the newborn. Maternal hyperglycaemia in GDM results in fetoplacental endothelial dysfunction. GDM-harmful effects result from chronic and short periods of hyperglycaemia. Thus, it is determinant to keep glycaemia within physiological ranges avoiding short but repetitive periods of hyper or hypoglycaemia. The variation of glycaemia over time is defined as 'glycaemia dynamics'. The latter concept regards with a variety of mechanisms and environmental conditions leading to blood glucose handling. In this review we summarized the different metrics for glycaemia dynamics derived from quantitative, plane distribution, amplitude, score values, variability estimation, and time series analysis. The potential application of the derived metrics from self-monitoring of blood glucose (SMBG) and continuous glucose monitoring (CGM) in the potential alterations of pregnancy outcome in GDM are discussed.

1. Introduction

A healthy human pregnancy is a physiological process characterised by the growing fetus's high demand for nutrients, including oxygen. Several factors are involved in keeping a favourable intrauterine environment for successful fetal growth and development [1–6]. Among many other factors, keeping the plasma level of D-glucose in a physiological range (~4.5–5 mmol/L) is critical. The mother and fetus' metabolism depend on the ability of cells to sense the extracellular level of D-glucose, modulating the expression and activity of membrane transporters and enzymes involved in the metabolism of this hexose. Unfortunately, a considerable number of pregnant women show D-glucose intolerance —a metabolic condition resulting in hyperglycaemia— and a deficient regulation of all body cells metabolism by

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insulin [3,4,7].

Pregnant women who show any degree of glucose intolerance detected for the first time in pregnancy by the end of the second trimester or after are diagnosed with gestational diabetes mellitus (GDM) [8]. Therefore, patients with GDM likely developed glucose intolerance already several weeks before detection. Patients with GDM show hyperglycaemia which subsequently leads to hyperinsulinemia and insulin resistance. It is conceived that maternal hyperglycaemia results in fetal hyperglycaemia and hyperinsulinemia [3,4,9,10], and a state of insulin resistance [3,4,7,11–13]. It is also reported that GDM associates with alterations in the fetoplacental vasculature supporting the notion that D-glucose intolerance already starts earlier in pregnancy These alterations are associated with endothelial dysfunction ([3,4,6,7,14]. However, since achieving normal glycaemia in the mother following GDM diagnosis does not result in restoring the GDM-associated fetoplacental vascular dysfunction, other factors than plasma or the interstitial D-glucose concentration may be involved [6,7,14].

Patients diagnosed with GDM are, in general, included in a group of women irrespective of their nutritional status and metabolic conditions [7]. Yet, obesity is a pandemic also affecting women of childbearing age [15–19], driving a higher prevalence of pre-pregnancy maternal obesity. Pre-pregnancy maternal obesity is a risk factor for developing GDM [1–4,7,9,10]. Therefore, women with GDM should be considered individuals with a pre-pregnancy status that could determine the impact of this disease of pregnancy in the mother and fetus differently. Based on the maternal pre-pregnancy body mass index (BMI), at least three distinct groups of women with GDM are differentiated, viz, women with normal pre-pregnancy weight (BMI 18.5–24.9 kg/m^2, referred to as classical GDM or GDM lean), pre-pregnancy overweight (BMI 25–29.9 kg/m^2) or pre-pregnancy obesity (BMI $\geq$30 kg/m^2, referred to as gestational diabesity [7,19–21].

A correlation between obesity and type 2 diabetes mellitus (T2DM) is reported [22–24] while the exact mechanisms behind obesity influencing the development of T2DM are still unclear. The metabolic condition of patients with T2DM and obesity was referred to as diabesity [22,23,25]. Patients with diabesity show a higher risk of developing cardiovascular disease and vascular dysfunction [22]. On the other hand, pregnant women with pre-pregnancy obesity that develop GDM are referred to as having gestational diabesity [7,19–21]. Patients under the subgroups GDM lean, GDM with pre-pregnancy overweight (GDM overweight), and gestational diabesity differ in their metabolic condition and in the aetiology of the alterations seen in their capacity to regulate the glycaemia [7].

GDM associates with variations of maternal glycaemia, showing different patterns over the time. The glycaemia increases after a glucose load (usually 75 g glucose) in women with GDM reaching higher levels than expected for women without alterations in glucose handling. However, a change in glycaemic status in GDM patients may refer to a higher than expected plasma glucose response to a glucose load as well as altered kinetics of increase and restoration of this hexose concentration after minutes or hours to physiological levels. Therefore, glycaemia variation along a time scale (over a repeated 24 h cycle for several days) is also a factor that should be considered in the characterization of a pregnant women at risk of GDM.

The variations of blood glucose concentrations due to changes in glucose metabolism over time in different tissues has been defined as 'glycaemia dynamics' [26]. Glycemia dynamics include the time that glycemia takes to reach values in a normal range, the time that glycemia remains in a hyperglycaemic state after feeding episodes, the flow patterns that appear over time [27], and the fluctuations and variability concerning time [28]. Different parameters are used to evaluate glycaemia dynamics according to the type of analysis used, viz, quantitative, plane distribution, amplitude, score values, variability estimation, and time series analysis.

The whole set of variations in the glycaemia, i.e. not only the value at 1 or 2 h after a glucose load, might represent a pattern of glycaemia dynamics that may be different in women with GDM compared with pregnant women with a normal pregnancy. As GDM associates with fetoplacental vascular dysfunction [6,7], glycaemia dynamics may contribute to the development of vascular dysfunction, both in the mother and fetus. The glycaemia dynamics may, however, show different patterns in women with gestational diabesity compared with GDM lean or GDM overweight.

Several monitoring schemes have been developed to estimate the changes over time in the capillary blood glucose levels for a better metabolic control of patients with diabetes mellitus. Despite presenting a delay compared with a single capillary blood glucose determination, continuous blood glucose monitoring (CGM) has become broadly used. CGM approach measures the interstitial fluid glucose concentration showing recordings almost identical to glycaemia values (with CGM recordings adequately calibrated) for stable glucose levels (rates of change of glucose level $<$ 1–2 mg/dL/min) [29] with a lag time of ~10 min regarding a change in the glucose of the blood change [29,30].

This review summarizes observations on the pattern and variations in the interstitial fluid glucose dynamics from data collected by a CGM approach in patients with diabetes mellitus emphasising what is known in women with diagnosis of GDM. A potential general interpretation of the different metrics derived from data collected by CGM is provided, and the correlation of these metrics with endothelial dysfunction and pregnancy outcomes are discussed.

2. Glycaemia dynamics and metrics of glucose monitoring in GDM

The glycaemia varies within physiological ranges and also regularly during the day related to moments of food intake and periods of fasting as wells as periods of physical activity and stress in healthy subjects allowing the supply of D-glucose to tissues as required for energy generation. Patients with diabetes mellitus show fluctuations in their glycaemia, which are different from the fluctuations seen in healthy subjects. In pregnant women, the general recommended procedure is to run an oral glucose tolerance test (OGTT) to decide whether they show glycaemia within the expected range for a normal, non-diabetic pregnancy (hereafter referred to as normal pregnancy) [8]. In the one-step strategy for OGTT after a 75 g glucose load the glycaemia in women with normal pregnancies are to meet $<$92 mg/dL (5.1 mmol/L) fasting, $<$180 mg/dL (10 mmol/L) 1 h post-load, and $<$ 153 mg/dL (8.5 mmol/L) 2 h post-load [8]. When any value is met or exceeded, women are diagnosed with GDM following recommendations from The International Association of the Diabetes and Pregnancy Study Groups (IADPSG) [31] and the American Diabetes Association [8].

During pregnancy, glycemia changes because of placental hormone release affecting insulin sensitivity. The inability of women with GDM to regulate their blood glucose levels results in hyperglycaemia. This abnormal metabolic condition significantly affects the fetus, which may increase the risk of metabolic disorders in infants, children, and adults. Pregnant women with GDM with poor or uncontrolled glycaemia fluctuations reach higher than recommended glycaemia values after a meal. These women may show basal as well as postprandial excess glycaemia, which may take longer to return to baseline. Higher basal glycaemia may result in a long-lasting exposure of the fetus to excess glucose, while postprandial excess glycaemia results in peaks of fetal glucose exposure. We expect basal and postprandial excess glycaemia's effects on fetal metabolism to be different since the dynamics of the exposure to hyperglycaemia are different both in duration as well as absolute levels. Thus, the fluctuations in maternal glycaemia configure repeated windows of exposure of the fetus, which could selectively alter its metabolism. In addition, changes in glycaemia dynamics in patients with GDM, including GDM lean, GDM overweight, and gestational diabesity differ, but have not been studied in much detail so far.

Several reports show that endothelial dysfunction is a consequence

of hyperglycaemia in subjects with diabetes mellitus. Interestingly, patients with diabetes mellitus with normal glycaemia and $HbA_{1c} < 6\%$ (in Diabetes Control and Complications Trial (DCCT) units) or < 42.1 mmol/mol (in International Federation of Clinical Chemistry (IFCC) units) (see https://www.diabetes.co.uk/hba1c-units-converter.html) due to therapeutic control also show endothelial dysfunction [14,32]. The endothelial dysfunction may therefore result from a high variability of the glycaemia dynamics, which correlates with the severity and duration of hyperglycaemia and hypoglycaemia events [33]. Several studies suggest that not only hyperglycaemia but also the alterations in the glycaemia dynamics relate to the development of pathologies associated with diabetes mellitus more than hyperglycaemia itself [34]. To date, glycaemia variability has been shown to be positively related to the risk of retinopathy and all-cause mortality in patients with T2DM [35] and cardiovascular autonomic neuropathy in patients with T1DM [36].

CGM approach is considered a valuable method for predicting hyperglycaemia and hypoglycaemia events [34]. A proper capillary glycaemia monitoring result from at least five measurements a day, and when the patient does it, it is referred to as self-monitoring of blood glucose (SMBG). However, with the development of new technologies enabling automated and more continuous estimations of glycemia, the SMBG approach for capillary glycaemia has been replaced by CGM approach for estimation of glycaemia based on the measurements of interstitial fluid glucose concentration [34,37].

CGM can facilitate patient's education and glycaemia monitoring [38]. With the development of continuous measurement instruments and sensors, large volumes of data are collected (Fig. 1). The analysis of this huge amount of data has great potential to improve the understanding of interstitial fluid glucose and glycaemia dynamics [39]. Indeed, different approaches are used to analyse glycaemia dynamics based either in SMBG or CGM recordings [37,40,41].

2.1. Joint data analysis

The collected data of the plasma glucose concentrations available for a patient over a specific period may be subjected to joint data analysis to obtain different metrics indicative of specific characteristics of the glycaemia dynamics. The joint data analysis metrics include the sample mean ($\overline{X}$), standard deviation (*SD*), coefficient of variation (*CV* or *%CV* when expressed as percentage), interquartile range (*IQR*), mean of daily differences (*MODD*), and time in range (*TIR* or *%TIR* when expressed as a percentage) (Table 1). These metrics are used to picture the status of the variations of glycaemia and efficiency of the therapeutic protocols applied in patients with diabetes mellitus.

The $\overline{X}$ refers to the average of the total number of glycaemia measurements performed in a defined period (usually 24 h) and is the most used parameter in the clinic [34] (Fig. 2A). In general, it is reported that a pregnant woman with normoglycaemia shows $\overline{X}$ ~95 mg/dL with ~99 and ~ 90 mg/dL for diurnal and nocturnal glycaemia, respectively [42]. It is considered that the closer a $\overline{X}$ value is to a defined threshold for glycaemia (usually ~92 mg/dL glucose) [8], the more stable is the glycaemia. A more stable glycaemia is for instance indicative of a proper control of the health status of a patient with diabetes mellitus. The $\overline{X}$ metric by itself is of low value and requires counting with the *SD* value. The *SD* metric shows the absolute dispersion of the glycaemia values compared with the $\overline{X}$ values. It is considered that the higher the *SD* value, the more unstable is the glycaemia and therefore the severity of the disease in patients with diabetes mellitus. However, *SD* value is highly dependent on extreme (higher and lower) and isolated values in a group of glycaemia measurements [37]. Thus, $\overline{X}$ and *SD* metrics may be useful for visualising the changes in glycaemia; however, these metrics are restricted to be single values that do not reflect the panorama in variability glycaemia in patients. Thus, the $\overline{X}$ and *SD* are not the best metrics to describe glycaemia dynamics in healthy subjects and in patients with diabetes mellitus.

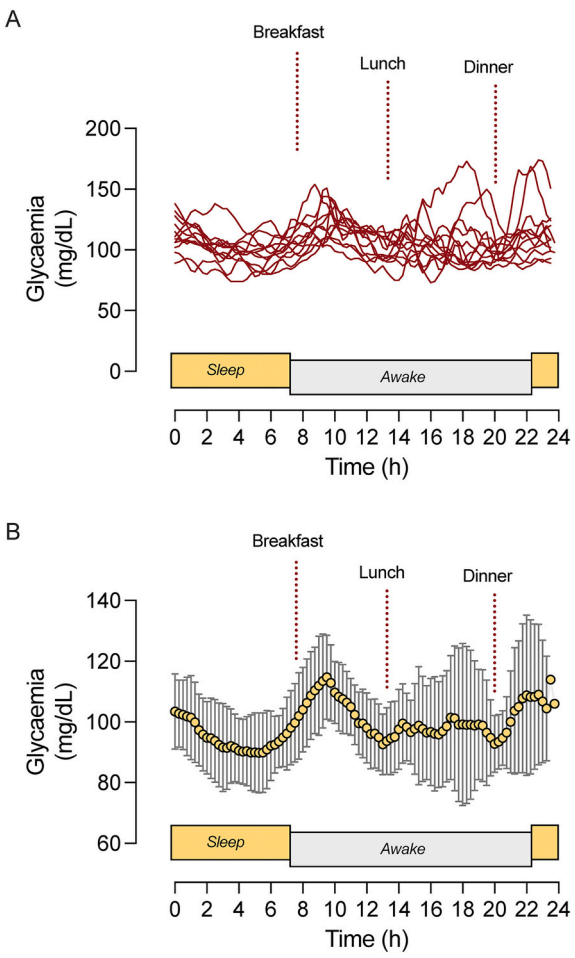

Fig. 1. Records of interstitial fluid glucose measured by continuous glucose monitoring approach. Interstitial fluid glucose concentration was determined in a 58-year-old healthy man using the continuous glucose monitoring (CGM) approach (FreeStyle Libre 14 day Flash Glucose Monitoring System, Abbot, CA, USA) for 12 days. The records shown are only as a graphical example (not for medical analysis). A. Twelve records of 24 h each are represented into a scale for one day. Each record shows the variations for night period (*Sleep*, 8½ h) and day period (*Awake*, 15½ h) including the moments of breakfast, lunch, and dinner. B. Mean and standard deviation for each time recorded for 12 days from data in A.

Estimating the variability in glycaemic values has gained ground compared with the determination of $\overline{X}$ and *SD* [34,43]. The *CV* corresponds to the variation of the *SD* for glycaemia values relative to the $\overline{X}$ value. The *CV* is expressed as percentage (*%CV*) and is used to estimate the effectiveness of diabetes management. Since the *CV* value derives from the *SD*, they are also highly affected by extreme and isolated values. As an example of the applicability of *CV* was reported in adult subjects showing a 24 h $\overline{X}$ ~105 mg/dL with *SD* ~ 21 mg/dL and a *%CV* 20, which was considered to show a good glycaemic control in these subjects [44]. Furthermore, these subjects showed lower values of *SD* (~18 mg/dL, i.e. ~14% reduction) and *%CV* (~17, i.e. ~15% reduction) during the night but maintained an unaltered $\overline{X}$ (~106 mg/dL) compared with values for the whole 24 h period [44]. Interestingly, patients with T2DM show higher values of 24 h $\overline{X}$ (~128 mg/dL) and *SD* (~25 mg/dL) but similar *%CV* (~20) compared to healthy subjects [45]. Thus, patients with T2DM are affected by higher glycaemia that seems to be with low variability for a defined period. However, these patients showed greater hardening of the aorta, likely due to endothelial dysfunction [45]. It is suggested that alterations in a combination of parameters, v.g. $\overline{X} + SD + \%CV$, more than each parameter individually

Table 1
Joint data analysis metrics for glycaemia dynamics.

Metric	Formula	Definition	General interpretation	References
Sample mean ($\overline{X}$)	$\overline{X} = \frac{\sum_{i=1}^{n} X_i}{n}$ X_i Single observation in a group of glucose concentration measurements n Total number of glucose concentration measurements	Arithmetic mean of a group of glucose concentration measurements.	The closer to a defined threshold for glucose concentration, the more stable is the glycaemia.	[52,125,126]
Standard deviation (*SD*)	$SD = \sqrt{\frac{\sum (X_i - \overline{X})^2}{n-1}}$ X_i Single observation in a group of glucose concentration measurements $\overline{X}$ Sample mean n Total number of glucose concentration measurements	Absolute values of dispersion of the glucose concentration measurements compared with the $\overline{X}$.	The greater *SD* of the group of glucose concentration measurements, the more unstable is the diabetes. This metric is highly sensible to extreme and isolated values.	[37]
Coefficient of variation (*CV*)	$CV = \frac{SD}{\overline{X}}$ *SD* Standard deviation $\overline{X}$ Sample mean	Normalization of the *SD* of the group of glucose concentration measurements against the $\overline{X}$.	Higher *CV* indicates high variability meaning that glucose concentration is unstable. This metric is highly sensible to extreme and isolated values.	[34,43]
Percentage of coefficient of variation *(%CV)*	$\%CV = \left(\frac{SD}{\overline{X}}\right) \bullet 100\%$ *SD* Standard deviation $\overline{X}$ Sample mean	Normalization of the *SD* of the group of glucose concentration measurements given as percentage of the $\overline{X}$.	*%CV* >36 indicates high variability meaning that glucose concentration is unstable and diabetes management may be out of control. This metric is highly sensible to extreme and isolated values.	[34,43]
Interquartile range (*IQR*)	$IQR = Q_3 - Q_1$ Q_1 1st quartile for glucose concentration corresponding to the 25% of measurements Q_3 3rd quartile for glucose concentration corresponding to the 75% of measurements	The difference of between Q_3 and Q_1 when ordered from the lowest to the highest measurements.	Higher IQR implies greater variability meaning that glucose concentration is unstable. This metric is more stable than *CV* and *%CV* to extreme and isolated values.	[34]
Mean of daily differences (*MODD*)	$MODD = \frac{\sum_{t=1}^{T} \lvert X_t - X_{t-1} \rvert}{T}$ X_t Glucose concentration measurement at time *t* in each day X_{t-1} Glucose concentration measurement at time *t* measured 24 h before the given day *t* Time t in each day *T* Number of days	Average of the absolute values of the differences between glucose concentrations measured in two consecutive days at the same time (i.e. inter-day variations) in a window of T days.	Shows the mean behavior of the inter-day glucose variability. The greater the *MODD* value, the more unstable diabetes.	[43,47,48]
Time in range (*%TIR*)	$\%TIR = \frac{\tau}{T} \bullet 100\%$ τ Period that glucose concentration values are within a defined recommended interval of glucose concentrations (target range) *T* Total time of the evaluation period	The absolute time that glucose concentration values are within a defined target range given as percentage of the T (usually 24 h).	Establishes the range of glucose concentration *cutoff* points (higher and lower) for an effective therapeutic decision-making for the treatment of patients with diabetes	[49,50]

may result in increased vascular function abnormalities.

A metric less affected by extreme and isolated values than *%CV* is the *IQR* [34]. *IQR* is the 50% of the total measurements of glycaemia located between 25 and 75% of the complete set of values (Fig. 2B). A higher *IQR* means higher variability of glycaemia values and, therefore, a deficient regulation of glycaemia in patients with diabetes mellitus. In women with normal pregnancies, an *IQR* ~ 23 mg/dL was reported [46]. Also, *IQR* values are helpful when compared with other metabolic conditions. To date, pregnant women with GDM treated with a controlled diet showed *IQR* ~ 27 mg/dL while women with GDM under insulin therapy showed *IQR* ~ 35 mg/dL. Furthermore, the *IQR* in women with pre-pregnancy diabetes mellitus was ~50 mg/dL [46]. Thus, *IQR* metric may serve as an intragroup (i.e. same pathology) or intergroup (i.e. different pathologies) comparison.

Broader ranges of glycaemia measurements considered in patients with diabetes mellitus within a fixed period of 24 h are estimated by the *MODD* [43,47,48]. *MODD* shows the absolute mean glycaemia at the same time of the day in two consecutive days and reflects day to day variations in glycaemia (Fig. 3). A higher *MODD* is indicative of a potentially unstable regulation of glycaemia and, therefore, an indication to improve the management of diabetes mellitus. However, *MODD* is of limited use since it assumes that the patient is continuously experiencing a stable, reproducible pattern of meals, physical activity, and medications on successive days [37]. *MODD* may be different according to the time of the day when measured or even it can be different when two consecutive determinations of this metric are done in the same individual.

A stronger association of the regulation of glycaemia and management of diabetes mellitus is given by the *%TIR*. This metric stands for the percentage of a total period of time with glycaemia values within a predefined range (high and low glycaemia) [49,50] (Fig. 4A). This metric has been used to implement and sharpen an effective therapeutic protocol for treating patients with diabetes mellitus. The *%TIR* helps to determine *cut-off* points, thus facilitating an effective therapeutic decision-making for patients. Interestingly, it was shown that in pregnant women with T1DM and T2DM, an increase by 5% of the time in range (v.g. 70–140 mg/dL, *%TIR* 5) was associated with clinical benefits even when the recommended *%TIR* were 43–56 [49]. The %*TIR* recommended in patients with T1DM and T2DM is at least 70%, with a time below target <4% and time above target <25% [49,51]. Unfortunately, a consensus on this metric has yet to be reached for women with GDM [49] and no further information is reported for possible differences between women with GDM lean, GDM overweight, or gestational diabesity [6,7].

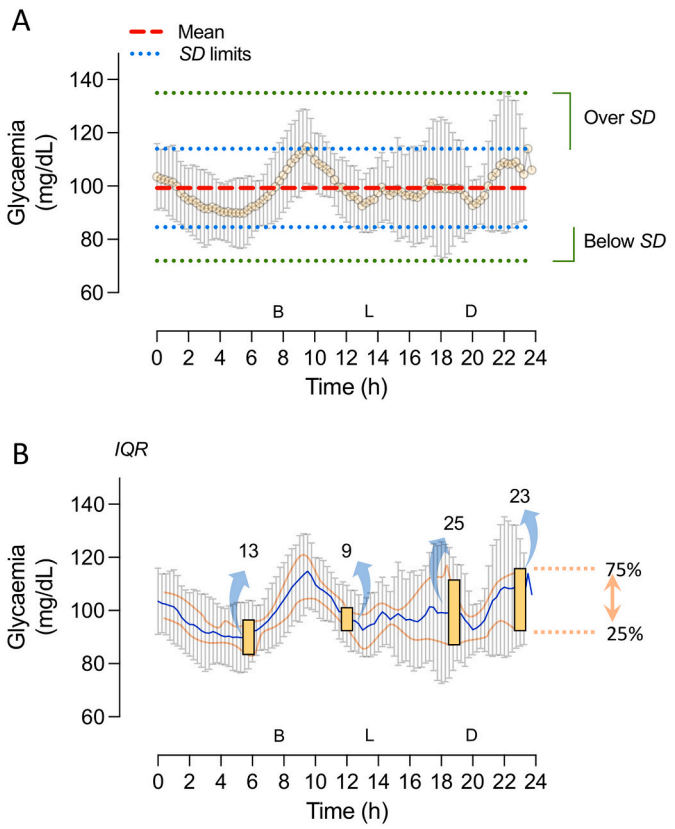

Fig. 2. Mean, standard deviation, and interquartile in the interstitial fluid glucose measured by continuous glucose monitoring approach. Interstitial fluid glucose concentration was determined in a 58-year-old healthy man using the continuous glucose monitoring (CGM) approach (FreeStyle Libre 14 day Flash Glucose Monitoring System, Abbot, CA, USA) for 12 days. Twelve records of 24 h each are represented into a scale for one day. The records shown are only as a graphical example (not for medical analysis). A. Mean ($\overline{X}$) and standard deviation (*SD*) values with plus *SD* and minus *SD* (*SD limits*) are represented. The maximal (*Over SD*) and minimum (*Lower SD*) values for *SD* are indicated. The $\overline{X}$ value was 98 mg/dL glucose and *SD* limits ±14 mg/dL glucose in this example. B. Graphical representation of the interquartile (*IQR*) for glycaemia between 75 and 25% of the SD limits shown in A. Values show the individual IQR values detected at four different times in 24 h. B, breakfast; L, lunch; D, dinner.

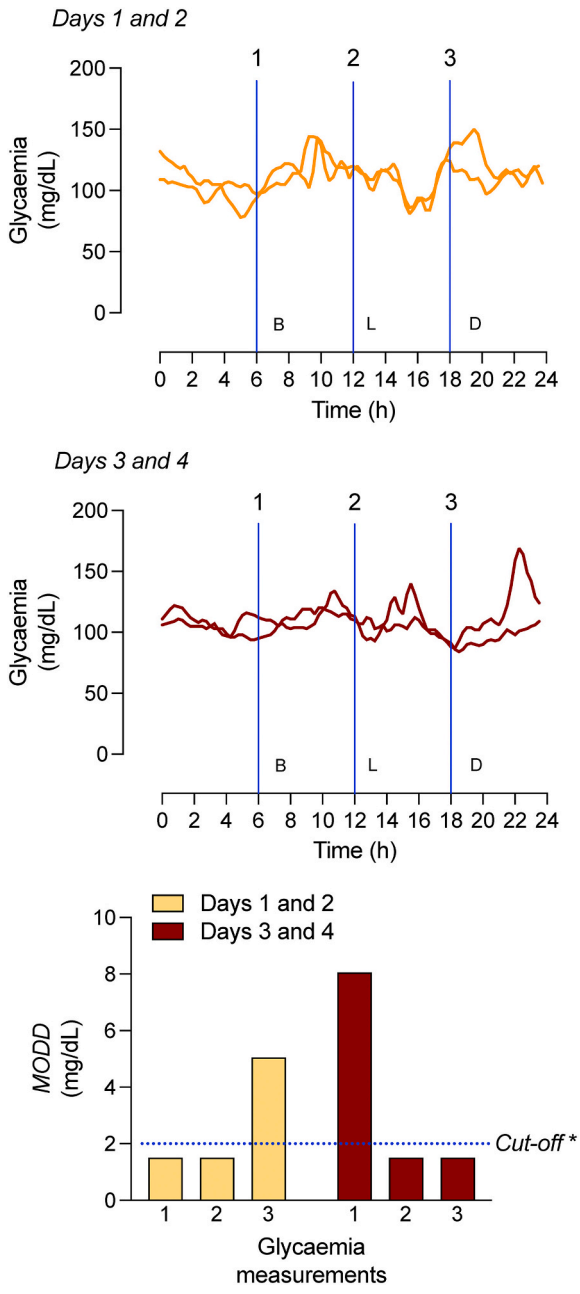

Fig. 3. Variable results for mean of daily differences in the interstitial fluid glucose. Interstitial fluid glucose concentration was determined in a 58-year-old healthy man using the continuous glucose monitoring (CGM) approach (FreeStyle Libre 14 day Flash Glucose Monitoring System, Abbot, CA, USA) for 4 consecutive days. The records shown are only as a graphical example (not for medical analysis). A. Interstitial glycaemia records for the first two days (*Days 1 and 2*) where glucose concentration was obtained at the same time at days 1 and 2 at 06:00 am (1), 12:00 (noon) (2), and 18:00 (3). B. Records for *Days 3 and 4* as in A. C. Mean of daily differences (*MODD*) calculated from A and B at 06:00 am (1), 12:00 (noon) (2), and 18:00 (3). *MODD* corresponded to half of the difference between days 1 and 2 or days 3 and 4 (see Table 1). The indicated cut-off (*MODD* 2) was arbitrary, and it is shown only as example to highlight the variability of *MODD* depending on the time of the day considered for the analysis. B, breakfast; L, lunch; D, dinner.

2.2. Plane distribution analysis

The metrics for the analysis of the distribution of glucose measurements in the plane, i.e. the Cartesian coordinate plane or graph, are summarized in Table 2. The frequency distribution (F_i) addresses the proportion of the measured glucose concentrations within a specific predefined range. This metric is the basis for the metric *%TIR*. Although the F_i provides more information than *%TIR*, it is considered a complex metric to interpret in the clinic [47–49]. The metric supplying more information on glycaemia dynamics in patients is the ambulatory glucose profile (*AGP*) (Fig. 1). *AGP* is a graph type metric only possible when CGM is applied [34]. The *AGP* shows a combined 2-weeks result of glycaemia dynamics and a daily overview in graphs. Also, *AGP* gives information on whether glycaemia management needs to be changed [52]. Under the international consensus for the use of CGM, the recommended approach for displaying continuous data of glycaemia is *AGP* [53].

The metric area under the curve (*AUC*) (Fig. 4B) is used to describe glycaemia dynamics in postprandial periods allowing the analysis of *cut-off* points in OGTT. Its clinical utility is limited to the diagnosis of diabetes compared with the study of the glycaemia dynamics or management of the disease [54]. However, when implemented, *AUC* values measured for 24 h provide useful information on the glycaemia in terms of its dynamics to compare between women with a normal pregnancy or with GDM [46].

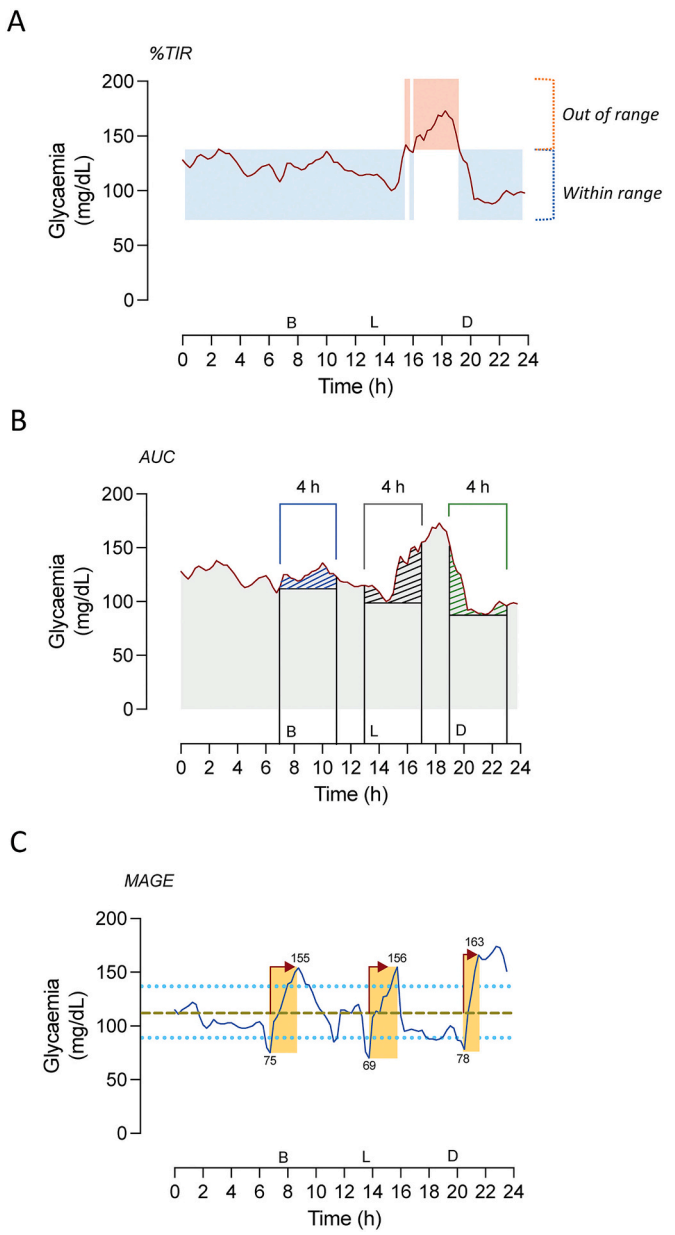

Fig. 4. Time in range, area under the curve, and mean amplitude of glucose excursion in the interstitial fluid glucose. Interstitial fluid glucose concentration was determined in a 58-year-old healthy man using the continuous glucose monitoring (CGM) approach (FreeStyle Libre 14 day Flash Glucose Monitoring System, Abbot, CA, USA) for 24 h. The records shown are only as a graphical example (not for medical analysis). A. Time in range (*%TIR*) for interstitial fluid glucose concentration showing areas of within (*Within range*) or, in this example, over (*Out of range*) a preestablished range (lower and higher concentrations). B. Area under the curve (*AUC*) derived for preestablished periods of 4 h (datched areas) from breakfast (B), lunch (L), or dinner (D) based on records as in A. Corresponding AUC values may be used for internal comparison (i.e. *AUC* for B versus L or D, and others) and to compare with another condition (v.g. exercise, medication, disease). C. Interstitial fluid glucose concentration used to estimate mean amplitude of glucose excursion (*MAGE*). The mean value ($\overline{X} = 112$ mg/dL, green line) and standard deviation (SD ± 26 mg/dL, light blue dotted lines) for the 24 h record of glucose concentration is shown and used as reference to calculate *MAGE* at three different times. Red arrows show the peak of interstitial fluid glucose concentration related to the $\overline{X}$ value in an excursion from the indicated nadirs to peaks (orange areas). B, breakfast; L, lunch; D, dinner. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

2.3. Amplitude, distribution, and frequency analysis

Other approaches used to estimate glycaemia dynamics is the analysis of amplitude and distribution of frequencies (Table 3). The mean amplitude of glucose excursion (*MAGE*) is one of the first metrics described in patients using the SMBG approach. *MAGE* allows calculating the amplitude of glycaemia excursions (increased or decreased values) in 24 h [37] (Fig. 4C). *MAGE* may be interpreted as how high (or intense) the hyperglycaemia is at a specific stage in the patient. *MAGE* metrics depends on the *SD* and is therefore subject to error since the *SD* varies over time [55]. In a relative recent study aimed to determine the reference values for CGM metrics in a group of 60 healthy subjects (including 70% women and 30% men) a *MAGE* of ~47 mg/dL during the day in 24 h recording was reported [44]. These patients also showed a lower *MAGE* (~39 mg/dL) during the night period, suggesting that the intensity of glycaemia and its potential harm consequences in these subjects is lower (~17% in this case) during the night.

Another approach used to estimate glycaemia dynamics includes the analysis of amplitude and distribution of frequencies (Table 3). One of these approaches is the metric distance traveled (*DT*), which captures the number of determinations, i.e. frequency, and the 24 h oscillations of glucose concentrations [56]. However, it is conceptually hard to understand the relevance for clinical practice, and therefore, of little use. In the analysis of a continuous monitoring reading in 11 patients (9 females and 2 males) with T1DM on insulin therapy, the *DT* ranged from 1496 to 3064 mg/dL resulting in a difference of 1568 mg/dL with a 2.05 fold increase from the lower glycaemia value. In comparison, *MAGE* ranges from 145 to 157 mg/dL giving a difference of 12 mg/dL with to 1.1 fold increase from the lower glycaemia value [40]. These findings reflect more variability in the *DT* metric (1.9 fold higher) than that reported by *MAGE* metric for the same patient.

2.4. Glucose score values

Due to the complexity of the data obtained with CGM, score values have been developed to classify the risk of patients with diabetes mellitus to develop this disease's associated complications. Table 4 describes the most used approaches for glucose score values. The low blood glucose index (*LBGI*) and high blood glucose index (*HBGI*) are helpful metrics for the estimation of the quality of glycaemic control [37]. In patients with T1DM or T2DM, *LBGI* < 2.5 or < 4.5, or *HBGI* > 5.0 or > 9.0 correspond to low or high risk of severe hypoglycaemia and hyperglycaemia, respectively [57,58]. In the absence of a standard measure to analyse the CGM-derived data and given the large number of metrics available, the use of the *%CV* together with *LBGI* and *HBGI* has been proposed in clinical practice [59]. It is reported that women with GDM show *HBGI* values ~2 fold higher than women with normal pregnancies in the second trimester of pregnancy [60]. Interestingly, this value for *HBGI* metric was shown to associate with altered newborn weight index in these pregnancies. Thus, exposure of the fetus to a high glycaemia variability is a determinant factor of fetal overgrowth.

The metric referred to as average daily risk range (*ADRR*) includes *LBGI* and *HBGI* values [47,48,61]. This metric shows the risk for glycaemia variability (*ADRR* < 20 is low risk, 20–40 is moderate risk, and > 40 is high risk) and is sensitive to hypoglycaemia excursions. Children with T1DM showed higher susceptibility to hypoglycaemia excursions making the *ADRR* a valuable metric for these patients [62].

The glycaemia risk assessment diabetes equation (*GRADE*) summarizes the degree of risk associated with a determined glucose profile [63]. Interestingly, this metric is not used in clinical practice. However, *GRADE* has enormous potential in figuring out the relationship between glycaemia dynamics and maternal-fetal pathologies. *GRADE* gives glycemia data providing a single value which defines the assessed clinical risk to which a patient is exposed. That is, it can provide weighted risk contributions from hypoglycaemia, euglycaemia, and hyperglycaemia and this can be related to the development of maternal-fetal pathologies

Table 2
Analysis of distribution in the plane for glycaemia dynamics.

Metrics	Formula	Definition	General interpretation	References
Frequency distribution (F_i)	$F_i = \frac{n_i}{N}$ n_i Total of number of glucose concentration measurements in the *i*-th interval N Total number of glucose concentration measurements	Glucose concentrations sorted by designated categories and plotted on a frequency histogram	Allows visualization of the values of the most frequent observations together with the dispersion of the records in an interval	[125,126]
Ambulatory glucose profile (*AGP*)	$\widetilde{X_q}(i) = median\,[u(i), v(i), w(i)]$ $u(i) = median\left\{X_q(i-1), \frac{[3 \bullet X_q(i-1) - X_q(i-2)]}{2}, X_q(i)\right\}$ $v(i) = median\,[X_q(i-1), X_q(i), X_q(i+1)]$ $w(i) = median\left\{X_q(i+1), \frac{[3 \bullet X_q(i+1) - X_q(i+2)]}{2}, X_q(i)\right\}$ $\widetilde{X_q}(i)$ The smoothed glucose concentration values at the 25th, 50th, and 75th percentile $X_q(i)$ The 25th, 50th, and 75th percentile glucose concentration values (q = 0.25, 0.50, 0.75)	It is a composite graph represented by three smoothed time series, obtained at the 25th, 50th, and 75th percentile of glucose concentration values of the day (Y-axis) versus time (X-axis).	This metric may facilitate systematic interpretation of data of glucose concentration monitoring the overall level of glycaemia control in terms of $\overline{X}$ (Table 1), the *%CV* (Table 1) related to *IQR* (Table 1), and the time of day showing the greatest hypoglycemia or hyperglycemia.	[127]
Area under the curve (*AUC*)	$AUC = \sum_{i=1}^{N} \frac{(X_i + X_{i-1})}{2}(t_i - t_{i-1})$ N Total number of glucose concentration measurements X_i *i*-th measurement of the glucose concentration at time t_i X_{i-1} *i*-th measurement of the glucose concentration at time t_{i-1} t_i *i*-th time t_i associated with the X_i measurement t_{i-1} *i*-th time t_{i-1} associated with the X_{i-1} measurement	It is the area under the curve of the observed glucose concentrations estimated by trapezoidal rule.	It is the measurement of postprandial glucose concentration. *AUC* quantifies the level of response to the feeding load.	[128,129]

Table 3
Amplitude and distribution of frequencies metrics for glycaemia dynamics.

Metrics	Formula	Definition	General interpretation	References
Mean amplitude of *glucose* excursion (*MAGE*)	$MAGE = \sum \frac{\lambda \bullet I(\lambda_i > v)}{K}$ $I(\lambda > v)$ Indicator function where it is 1 if λ is greater than one standard deviation of the glucose concentration in a 24 h period, and 0 otherwise λ Amplitude between the mean and peak of glycaemia (nadir-peak or peak-nadir) v One standard deviation of the mean glucose concentration in 24 h K Number of events such that $\lambda > v$	Arithmetic mean of adjacent (sequential) amplitudes whose magnitudes are higher than one standard deviation from the mean in 24 h.	Gives information about the normal or pathological levels of glucose concentration and allows characterization of glycaemia instability.	[41,43,58,130]
Distance traveled (*DT*)	$DT = \sum_{i=1}^{N} \lvert(X_i - X_{i-1})\rvert$ X_i Daily glucose concentration measurements at time *i* X_{i-1} Daily glucose concentration measurements at time *i*-1 N Number of observations or data points	It is the sum of the absolute differences in glucose levels from successive measurements over a day.	Quantifies the total change in glucose concentration over a period of time. The greater *DT* value the greater the variability.	[40,56]

[63]. The *Q-score* is useful in scanning continuous glucose monitoring profiles. It is developed to classify patients into at least five categories of metabolic control, viz, *Q-score* < 4 is considered very good, 4–5.9 is good, 6–8.4 is satisfactory, 8.5–11.9 is fair, and ≥ 12 is poor [64]. Thus, *Q-score* allows detecting those patients with diabetes mellitus that may require changes in the applied therapeutic action. *Q-score* is also useful when showing parameters associated with a type of therapeutic protocol that could be modified for optimizing patient-tailored therapies.

2.5. Variability estimation analysis

Based on the CGM data, several metrics have also been developed allowing the analysis of the glycaemia variability (Table 5). The way to apply the methods for estimation of variability are possible using CGM data and bioinformatics, so the use in the clinic is limited [47,48,53]. The mean absolute glucose (*MAG*) gives the absolute change in glucose concentration per unit of time. *MAG* is useful to estimate postprandial glycaemia changes depending on the selected time points but shows a poor correlation with *%CV* and *SD* for the differences in glycaemia [37]. Another metric, the continuous overall net glycaemia action (*CONGA*), allows estimating inter-daily variability, and high values indicate higher variation in glycaemia [65]. One aspect to have in mind when estimating *CONGA* metrics is that it assumes that the patients continuously experience a stable and reproducible pattern of meals, exercise, and medication [37]. It is reported that *CONGA* estimation in pregnant women with T1DM showed a correlation with a tendency to a higher neonate's ponderal index in the second trimester of pregnancy [60].

On the other hand, the metric glucose variability percentage (*GVP*) is highly related to *MAG* and *DT* but it is not often used in the clinic [37]. However, *GVP* captures the amplitude and frequency of the glycaemia oscillations [56]. The analysis of this metric in patients with T1DM using a bi-hormonal closed-loop system showed that *SD* and *MAGE* values were lower, but *GVP* values were higher, supporting this metric as a potential approach to estimate the variations of glycaemia in these

Table 4
Metrics for the analysis of glycaemic dynamics using scores of glucose values.

Metrics	Formula	Definition	General interpretation	References
Low blood glucose index (*LBGI*)	$LBGI = \frac{1}{N}\sum_{i=1}^{N} rl(X_i)$ $rl(X_i) = 22.77 \bullet f(X_i)^2$ *if* $f(X_i) < 0$, *and* 0 *otherwise* where $f(X_i) = ln(X_i)^{1.084} - 5.381$ for blood glucose readings in mg/dL N Number of glucose concentration measurements within a day rl Risk of hypoglycaemia	Non-linear transformation of the blood glucose concentration scale that apply symmetry to the subject's glycemia distribution.	High values indicate higher or longer hypoglycaemia events.	[131]
High blood glucose index (*HBGI*)	$HBGI = \frac{1}{N}\sum_{i=1}^{N} rh(X_i)$ $rh(X_i) = 22.77 \bullet f(X_i)^2$ *if* $f(X_i) > 0$, *and* 0 *otherwise* where $f(X_i) = ln(X_i)^{1.084} - 5.381$ for blood glucose readings in mg/dL N Number of glucose concentration measurements within a day rh Risk of hyperglycaemia	Non-linear transformations of the blood glucose concentration scale that apply symmetry to the subject's glycaemic distribution.	High values indicate higher or longer hyperglycaemic events.	[131]
Average daily risk range (*ADRR*)	$ADRR = \frac{1}{D}\sum_{d=1}^{D} LR^d + HR^d$ $LR^d = max\ (rl(X_1), \ldots, rl(X_N))$ and $HR^d = max\ (rh(X_1), \ldots, rh(X_N))$ for blood glucose readings $X_1, \ldots X_N$ taken within a day #d, $d = 1, \ldots, D$ N Number of glucose concentration measurements within a day D Total number of days d Specific day between 1 and D X_i i-th measurement of glycaemia X_N N-th measurement of glycaemia	Risk assessment of the total blood glucose variation in a risk space in a day defined as the average sum of *HBGI* for maximum glucose and *LBGI* for minimum glucose.	A value of 11.5 is sign of severe risk.	[48,131]
Glycaemic risk assessment diabetes equation (*GRADE*)	$GRADE = 425 \bullet [log_{10}(log_{10}(X_i \bullet 18) + 0.16)]^2$ X_i i-th measurement of glycaemia in mg/dL	Summarizes the risk associated with a glucose profile.	Highly correlated with *%TIR* (see Table 1).	[48,63]
Q-Score (*Q-score*)	$Qscore = 8 + \frac{\overline{X} - 7.8}{1.7} + \frac{Range - 7.5}{2.9} + \frac{t_{G(\langle 3.9)} - 0.6}{2.9} + \frac{t_{G>8.9} - 6.2}{5.7} + \frac{MODD - 1.8}{0.9}$ *Range* refers to <3.9, >3.9 to <8.9, and >8.9 mmol/L glucose as hypoglycaemia, euglycaemia, and hyperglycaemia, respectively $t_{G(<3.9)}$ Time in glycaemia <3.9 mmol/L $t_{G>8.9}$ Time in glycemia >8.9 mmol/L $\overline{X}$ Sample mean (see Table 1) *MODD* Mean of daily differences (see Table 1)	Based on a factor analysis using Z-score combined with the average *Range*, time in hyperglycaemia, time in hypoglycaemia, and *MODD* (see Table 1).	Characterizes glycaemia recorded data in categories and quality of glycaemia. <4 Very good (glycaemia completely within the target range) 4-5.9 Good (80-100% within the target range) 6.0-8.4 Satisfactory (partially outside the range with 20-50% in target range) 8.5-11.9 Fair (often outside the range with 50-80% outside target range) ≥12.0 Poor (>80% outside the range)	[132]

patients [37,56]. The mean absolute relative difference (*MARD*) is another metric referring the average of error values to a known reference value of glucose concentration (Table 5). *MARD* value figures out the accuracy of CGM sensors measuring interstitial blood glucose levels compared to a series of reference samples from SMBG data. A low value (expressed in percentage) of *MARD* stands for better sensor performance. A *MARD* of 10% has been reported to represent the level of precision required for the safe use of CGM devices [66].

2.6. Analysis of time series

Different approaches in the literature, such as *Fourier*, detrended fluctuation analysis (*DFA*), *Periodogram*, *SampEn*, and multiscale sample entropy (*MSE*) analysis use time series for the analysis of the glycaemia dynamics (Table 6). The *Periodogram* studies frequency oscillations and helps to understand the intricate regulation of glycaemia by, for example, insulin and the glycaemia dynamics in patients with diabetes mellitus; however, its clinical utility is limited due to the difficulty of interpreting the results [67]. The *DFA* metric estimates the degree of correlation within the recorded signal, i.e. glucose concentrations, analyzing the divergence between the time series and their linear regression in the studied time window [68,69]. It is proposed that this type of analysis makes possible to estimate the loss of complexity in the glycaemia dynamics due to dysregulated glucose homeostasis from where other methods have been developed, including *SampEn* [37]. Complexity analysis such as *SampEn* helps understand the fine regulation of glycaemia between subjects without or with diabetes mellitus. However, this type of analysis is more useful in research than in the clinic due to its complex interpretation in terms of diabetic pathology.

The multiscale sample entropy (*MSE*) metric is an index representing the glycaemia complexity during a defined period [70]. The scale factor for *MSE* analysis is arbitrary, so the complexity index varies between different reports. The *MSE* index is inversely correlated with changes in the glycaemia. The most widely used scale factor is up to 7 and low values for *MSE* indicate good control of the disease. More significant changes in *MSE* for glycaemia have been reported to increase the risk of developing macrovascular and microvascular pathologies characteristic of diabetes mellitus and suggest the degree of a dysfunctional glycaemia regulation among patients who have similar glycaemic control [28,37].

The *Fourier* analysis allows the extraction of characteristics of the glycaemia dynamics in a time series. It has helped to identify poor control of diabetes mellitus, therefore predicting the development of associated conditions such as endothelial dysfunction [71]. *Fourier's* derived lower energy of total variability is detected in patients with a

Table 5
Metrics for the analysis of glycaemic dynamics using variability estimation.

Metrics	Formula	Definition	General interpretation	References
Mean absolute relative deviation (*MARD*)	$MARD = \frac{1}{N}\sum_{i=1}^{N}\frac{\lvert CGM_i - SMBG_i\rvert}{SMBG_i} \bullet 100\%$ *CGM* Continuous glucose monitoring data *SMBG* Self-monitoring of blood glucose data *N* Number of glucose concentration measurements *i* i-th number of glucose concentration measurements	Percentage of the average of individual absolute relative errors for a reference value of glucose concentration.	It refers to whether a particular reading value of glucose concentration is high or low compared to a reference value. A percentage higher than 10% implies a significant difference compared to the reference value estimated by data from SMBG approach.	[133,134]
Continuous overall net glycaemic action (*CONGA*)	$CONGA = \sqrt{\frac{\sum_{t=t_1}^{t_i}(D_t - \overline{D})^2}{k^* - 1}}$ $D_t = X_t - X_{t-m}$ $\overline{D} = \frac{\sum_{t=t_1}^{t_{k^*}} D_t}{k^*}$ k^* Number of glucose concentration measurements to which there is a measurement 60 min before D_t Difference between glycaemia at time *t* and *t* minus *m* hours ago	Shows the standard deviation of the differences between values in a current observation and another value measured in a certain quantity of earlier hours. It is referred as to the intra-day glycaemic variation.	High values show greater glycaemic variation meaning that diabetes management is out of control and glucose concentration is unstable.	[43,65]
Glucose variability percentage (*GVP*)	$GVP = \left(\frac{L}{T_0} - 1\right) \bullet 100\%$ $L = \sum_{i=1}^{N}\sqrt{\Delta X_i^2 + \Delta T_i^2}$ $T_0 = \sum_{i=1}^{N}\Delta T_i$ *L* Length of the line representing the change of glucose concentration T_0 Length of the line representing the time duration of the glucose concentration measurement $\Delta Xi = X_i - X_{i-1}$ Difference of blood glucose concentrations $\Delta Ti = T_i - T_{i-1}$ Difference of time in the blood glucose concentration measurements *i* i-th number of glycaemia measurements *N* Number of glucose concentration measurements	Calculate the length of the time trace of a continuous glucose monitoring data set divided by the duration time in evaluation. It is expressed as a percentage.	Allows the detection of rapid oscillation frequency of glucose measurements.	[56]
Mean absolute glucose change per unit of time (*MAG*)	$MAG = \sum_{i=1}^{N}\frac{\lvert \Delta Xi\rvert}{\Delta Ti}$ $\Delta Xi = X_i - X_{i-1}$ Difference of blood glucose concentrations $\Delta Ti = T_i - T_{i-1}$ Difference of time in the blood glucose concentration measurements *i* i-th number of glycaemia measurements *N* Number of glucose concentration measurements	It is the sum of all absolute glycaemic changes relative to the time period over which the measurement was done.	This metric depends on the units of measurement for a time span and is poorly correlated with *SD* (see Table 1) and *MAGE* (see Table 3)	[135,136]

longer time from diagnosis of T1DM. These patients are considered as a population with a greater probability of comorbidity by developing pathologies associated with diabetes mellitus [71–73]. Despite the better information on glycaemia dynamics, the *Fourier* series analyses is not especially useful in the clinic since their interpretation requires complex bioinformatic analysis. However, it is helpful in research to develop new metrics or scores that consider oscillations, frequencies, and glycaemia variability resulting in tools that may be more practical for making medical decisions.

3. Glycaemia dynamics in diabetes mellitus

3.1. GDM

Despite the significant advances made in the analysis of CGM data, there are few reports associating interstitial fluid glucose and glycaemia dynamics with endothelial dysfunction in pregnant women that develop GDM. It has been reported that women with GDM have more extended periods of hyperglycaemia compared with non-pregnant, healthy women showing changes in glycaemia [74]. Thus, GDM may not only associate with a higher value of hyperglycaemia but also with an extended period in this abnormal condition when compared with non-pregnant women with normoglycaemia. It is reported that ~23% of women with GDM showed the lowest glycaemia value between midnight (i.e. 00:01 am) and 03:00 am, while ~43% of the patients showed the highest glycaemia value between 06:00–10:00 am [75]. Thus, hyperglycaemia events in patients with GDM occurring early in the morning may be a factor affecting the pregnant woman and fetus health.

Data obtained with the CGM approach in women with GDM revealed a more extensive time above the recommended glycaemia range after lunch, and positive correlation with the probability of macrosomia and

Table 6
Computational methods for the analysis of glycemic dynamics.

Method	Formula	Definition	General interpretation	References
Detrended fluctuation analysis (*DFA*)	$f(n) = \sqrt{\frac{1}{N}\sum_{k=1}^{N}\left[y(k) - y_n(k)\right]^2}$ $y(k) = \sum_{i=1}^{k}[B_i - \overline{B}]$ N Number of boxes of an equal length of which the time series is divided. A least-squares line is fit to data representing the trend in that box f(n) Calculated value for each box of the time series B_i The i-th interbeat interval $\overline{B}$ Average interbeat interval K Count of interbeats i The i-th interbeat $y(k)$ Integrated interbeat interval time series $y_n(k)$ Estimated trend of $y(k)$	This approach quantifies the long-term correlations of non-stationary time series and assesses the fluctuations of glucose concentration in the daily life in adult subjects without or with diagnose of diabetes mellitus. *DFA* also allows the study of the initial phases of a dysfunctional glucose metabolism.	Allows the detection of long-range correlations embedded in a seemingly nonstationary time series and avoids the spurious detection of apparent long-range correlations that are an artifact of non-stationarity. It has been used to predict the development of diabetes mellitus in patients at risk and to estimate insulin resistance in subjects without or with diagnose of diabetes mellitus.	[68,69]
Entropy sample (*SampEn*)	$SampEn = -log\left[\frac{B^{m+1}(r)}{B^m(r)}\right]$ $B^m(r) = \frac{1}{N-m}\sum_{i=1}^{N-m}Bi^m(r)$ N Length of a time series x where $x = \{x_1, x_2, x_3, \cdots, x_N\}$ m Length of the subsequence $x_i = \{x_{i+1}, x_{i+2}, \cdots, x_{i+m-1}\}$ of the time series of glucose concentration r Threshold of the maximum permitted distance B_i Number of times that the difference between two subsequence exceeds the threshold r $B_i^m(r)$ Average of the number of times that the difference is higher than the threshold r at different interval times $B_i^{m+1}(r)$ Average of the number of times that the difference is higher than the threshold r at different interval times of length m and $m+1$, respectively	This method is designed to characterize the level of irregularity, complexity, chance, and predictability found in time series. It is a derivative multiscale entropy used to study the complexity of glucose dynamics in patients with diabetes mellitus.	This method allows to distinguish between classes or groups of subjects, under different conditions in terms of record length, artifacts and border effects, i.e. classify subjects who have had more or less time with the disease	[137]
Multiscale sample entropy (*MSE*)	$y_j^{(\tau)} = \frac{1}{\tau}\sum_{i=(j-1)\tau+1}^{j\tau}x_i$ τ The scale factor and $1 < j < N/\tau$ N/τ Length of the resulting coarse grained time series y_j y_j The coarse-grained time series obtained with a moving average window of the original time series x_i The original time series of glucose measurements j Index of the j-th subsequence of the time series	This method is a statistical approximation of the time series analysis of continuous glucose monitoring, based on the complexity of the measurements and the *SampEn*. It is a derivation of a set of time series made from the glucose signal at different time scales using the coarse grain technique. *SampEn* values are calculated for each time series and are plotted with the corresponding scale factor to obtain a *MSE* index being the sum of the scale over the range of 1 to 7.	This approach has the potential to assess how treatment modalities can modify the dynamics of glucose variability because it generates a quality score to the dynamic measures of glucose time series. In this score, low values on the *MSE* scale indicate glycemia with high variability.	[132]
Fourier analysis (*Fourier*)	$F(t) = m + \sum_i\left\{C_i cos\left(2\pi\, i\, \frac{t}{24}\right) + S_i\, sin\left(2\pi\, i\, \frac{t}{24}\right)\right\}$ $m = \frac{AUC}{24}$ $F(t)$ The approximation using Fourier series C_i Amplitude coefficients related to the cosine harmonic cycles S_i Amplitude coefficients related to the sine harmonic cycles i The i-th harmonic cycle t Time of the glucose measurement 24 The period in hours considered assuming that every day is repeated m The amplitude media of the signal AUC Area under the curve	The method computes approximation of the signal using the Fourier series of the continuous glucose monitoring data. It is a linear combination that has as constant the *AUC* (see Table 2) over 24 h (*AUC*/24) and several harmonic curves where each component of the curve oscillates at a regular integral number of cycles in 24 h.	It can be used in relation to any clinical outcome whether related to average glycemic exposure precipitous glucose decreases, low glucose values, or perhaps for oxidative stress, particularly high glucose values	[71,72,73]
Analysis of diurnal variation using the	$S\left(\frac{k}{NT}\right) = \left\lvert\sum_n x_N[n] \bullet e^{-i2\pi\frac{kn}{N}}\right\rvert^2$	This approach consists of building a best-fit curve using repeated periodogram calculations. The periodogram is an	This method detects the circadian variation. The acrophased and nardis are the times of occurrence of maxima and	[138]

(*continued on next page*)

Table 6 (*continued*)

Method	Formula		Definition	General interpretation	References
periodogram method (*Periodogram*)	k	It is an integer and corresponds to the harmonic component	estimate of the spectral density of a signal. It is used to detect and estimate the possible significant periodic components in the CGM readings.	minima in the best-fit curve. These calculations provide a global definition of the temporal relationship between glucose concentration and insulin oscillations. The equation indicates whether the rises and falls in plasma levels tend to occur simultaneously or whether changes in one of the variables tend to precede or follow the other.	
	i	The complex number $\sqrt{-1}$			
	x_N	A periodic signal			
	N	Number of total samples by period			
	T	The period			
	n	The count of samples			
	π	π number			
Algorithms for pulse identifications (*ULTRA*)	Step 1: data input. The series of hormonal values are entered. Step 2: data preparation. Missing data are interpolated linearly. Step 3: elimination of nonsignificant changes. All changes in glucose concentration that do not meet the criteria for significance are eliminated, resulting in a clean profile. Step 4: calculation of pulse characteristics. For each pulse, the ascending portion, the descending portion, the total duration, the absolute and relative increment, the absolute and relative decrement, and the apparent half-life are calculated. Step 5: calculation of statistics for pulse parameters. The mean, standard deviation, and median of the pulse parameters obtained in step 4 are calculated for the set of pulses detected.		This approach is used for the analysis of the ultradian fluctuations of plasma glucose and insulin concentrations. The method computes the pulse identification that eliminates all peaks of glucose concentration for which either the increment or the decrement does not exceed a certain threshold. Pulse increment is defined as the difference between the level at the peak and the level at the preceding trough. Pulse duration is defined as the time interval separating the preceding and following troughs.	This method gives information of the oscillations and frequencies of glucose and/o insulin concentrations in relation to time. The method indicates whether the rises and falls in plasma glucose concentration tend to occur simultaneously or whether changes in one of the variables tend to precede or follow the other variable.	[67]

being large for gestational age [76]. These findings suggest a lower *%TIR* as a consequence of the disease. Interestingly, and as example of the utility of CGM data, almost ~23% of women with GDM were detected to be in need of insulin administration to normalise their glycaemia after meals. Interestingly, the number of patients using the CGM approach that needed insulin therapy was like that of patients requiring insulin under the SMBG approach [77]. However, CGM showed higher sensibility than SMBG at early pregnancy (26 weeks of gestation) since the proportion of women needing insulin therapy was ~2.3 fold higher under CGM (~28%) compared with SMBG (~12%) approaches [77]. There was no correlation between insulin requirement and the $\overline{X}$, *SD*, *MAGE*, and *MODD* metrics for glycaemia dynamics in the latter study. Thus, these metrics are to be taken with caution in patients with GDM when recorded in early pregnancy.

MAGE metric in a group of Chinese patients with GDM was considered an independent risk factor for preeclampsia [77]. The association between changes in glycaemia and preeclampsia suggests that altered glycaemia dynamics might result in harming the fetoplacental vascular function leading to preeclampsia. Also, women with GDM under insulin therapy monitored for 72 h by the CGM approach showed higher variability in glycaemia than patients treated with diet modifications or women with normal pregnancies [78]. The latter study showed that even when women had $\overline{X}$ ~90 mg/dL glucose, the time in hypoglycaemia (~370 min) and hyperglycaemia (~394 min) were higher than in patients with diet-controlled GDM [78]. Unfortunately, since time series analysis was not performed to the data obtained from these patients the modelling the glycaemia dynamics is unavailable. Altogether these findings add to evidence suggesting that altered glycaemia dynamics associate with adverse pregnancy outcomes (Fig. 5).

Women with GDM subjected to insulin therapy showed a higher time in hyperglycaemia by ~2.5 fold overnight (00:00 am to 06:00 am) and ~ 2.3 fold daytime (06:00 am to 12:00 pm) compared with women with this disease that were not treated with insulin [79]. Unfortunately, the reasons for these changes were not addressed in the latter study. Yet,

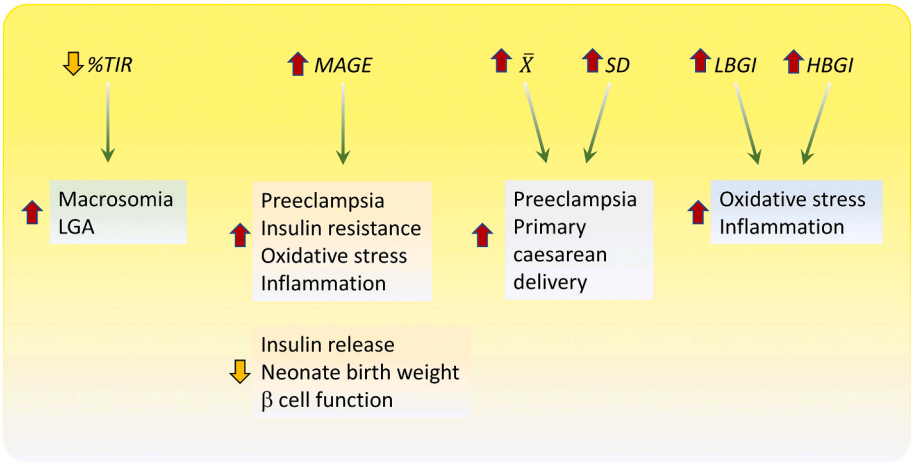

Fig. 5. Summary of the potential associations between glycaemia dynamics and pregnancy outcome in gestational diabetes mellitus. A decrease (↓) or increase (↑) in the indicated glycaemia dynamics metrics result in increased or decreased development of the indicated conditions. *%TIR*, time in range; *MAGE*, mean amplitude of glucose excursion; $\overline{X}$, mean; *SD*, standard deviation; *LBG*, low blood glucose index; *HBGI*, high blood glucose index; LGA, large for gestational age.

patients under insulin therapy showed higher BMI at 12 and 28 weeks of gestation (~30 and ~ 32 kg/m^2, respectively) compared with women without insulin therapy (~25 and ~ 28 kg/m^2, respectively) [79], suggesting additional impact of pre-pregnancy BMI on the needs of a particular treatment in these patients. Thus, lower *%TIR* in patients with GDM under insulin therapy may result from a joint action of insulin administration and higher pregnancy BMI. Unfortunately, a role for supraphysiological gestational weight gain in response to insulin therapy was not addressed in these studies.

Interestingly, patients with GDM subjected to insulin therapy show normoglycaemia because the efficient regulation of plasma glucose concentration by insulin. However, several alterations in the function of the placental vascular endothelial function and placental vascular reactivity are still present in these patients [80]. Furthermore, pre-pregnancy maternal obesity and overweight may also drive malfunction of the fetoplacental unit even after achieving normoglycaemia following insulin therapy [81]. Gestational diabesity is a metabolic condition that might result in a different behavior of glycaemia regulation compared with GDM lean [7,19,20]. Consequently, it seems necessary that women with GDM lean, GDM overweight, and gestational diabesity are evaluated separately for estimation of glycaemia dynamics. The latter is a consideration that is not limited to patients using the CGM approach only, since women with gestational diabesity under insulin therapy showed hyperglycaemia at fasting (>100 mg/dL) and post-breakfast (>200 mg/dL) when using the SMBG approach [79].

Pregnant women with T1DM who used insulin pump and were in the 24th week of gestation showed ~7% more time in hyperglycaemia episodes during the night (00:00 am to 06:00 am) compared with ~2% during the day (06:01 am to 12:00 pm) [82]. Interestingly, a subgroup of women for the latter study that received insulin injection showed no changes in the *%TIR* overnight but ~2% more time of hyperglycaemia during the day. These findings may reflect differential insulin responsiveness of the body to regulate glycaemia but may also result from the different administration routes of insulin at early gestation [82]. Furthermore, women using the insulin pump showed a poor pregnancy outcome associated with higher incidence of neonatal hypoglycaemia and higher neonatal intensive care admissions than women under daily insulin injections [82,83]. These findings suggest differences in temporal glucose concentration parameters in these patients, which may have been undetectable by CGM [81].

3.2. T1DM and T2DM

Even when patients with diabetes mellitus may show glycaemia and glycosylated haemoglobin A1c (HbA1c) levels within the expected normal ranges, some studies report endothelial dysfunction in these patients [32]. The latter may result from altered glycaemia dynamics as a more relevant factor than a single glycaemia determination in a fix period or measurement of HbA1c level which reflects the average plasma glucose concentration over the previous 2–3 months. At present, several metrics derived from the CGM approach have been related to endothelial dysfunction in patients with T1DM and T2DM [84,85]. Interestingly, glycaemia dynamics are not only useful in patients with diabetes mellitus but may also reflect the metabolic state of normal, without diabetes subjects. To date, it was reported that subjects without diabetes mellitus showed increased *MAGE* and altered endothelial function. These patients were at risk factor for cardiovascular events and coronary plaque vulnerability [86]. It is also reported that *SD* and *MAGE* are better correlated than *CONGA-1* (continuous overall net glycaemic action measured at 1 h period) and *MODD* metrics with coronary plaque vulnerability and risk of coronary artery disease in normal subjects, individuals with impaired glucose tolerance, and in patients with a diagnosis of diabetes mellitus [87].

Patients with T2DM also show enhanced *MAGE*, *MODD* and incremental *AUC* below 70 mg/dL [41]. These alterations in the glucose fluctuations were negatively associated with the flow and endothelium-dependent dilation of the brachial artery and positively related to C-reactive protein and insulin resistance. Also, patients with T2DM showing high $\overline{X}$ but low *%CV* for glycaemia had flow-mediated dilation and carotid intima-media thickness similar to subjects with low $\overline{X}$ but high *%CV* [88]. The results in the latter study suggest that the variation of the glycemia is critical in affecting the endothelial function confirming earlier reports in these patients [89]. Even more, a higher *SD*, *MAGE*, and *%TIR* correlates with vascular endothelial dysfunction in T2DM patients [90]. Other studies have concluded that altered glycaemia dynamics with a high *%CV* may have a higher impact leading to endothelial dysfunction than hyperglycaemia. Interestingly, patients with T2DM with *SD* of 1.4 mmol/L (~25.2 mg/dL glucose), *%CV* of 19.9, and low *%TIR* (~94) show a more significant hardening of the aorta suggestive of greater endothelial dysfunction [45]. The latter is an observation that could be useful in the interpretation of the potential deleterious effect of maternal hyperglycaemia in pregnancy on fetal vascular function. In GDM pregnancies, factor(s) other than only the maternal hyperglycaemia may result in alterations in the fetoplacental endothelial function since the glycaemia of the mother and newborn are within normal ranges at delivery [12,80]. One of these factors may be a large glycaemia variability during pregnancy rather than only an increased concentration of the glucose of the blood.

4. Oxidative stress and glycaemia dynamics in diabetes mellitus

Oxidative stress results from the loss of balance between a prooxidant and antioxidant state of the cells favouring the production of reactive oxygen species (ROS) and a decrease in antioxidant mechanisms [91]. In patients with diabetes mellitus, the oxidative stress is intensified by hyperglycaemia, and more specifically, a recurrent intermittent rather than sustained hyperglycaemia [92]. The latter is a phenomenon that could respond to changes in serum glucose within a single day [93]. The potential relationship between the changes in glycaemia and increased oxidative stress has been shown in vitro assays and experimental models of GDM, T1DM, and T2DM. Most studies report the combined effects of hyperglycaemia and hypoglycaemia peaks and their consequences associated with endothelial dysfunction and cardiovascular damage [94,95].

Human umbilical vein endothelial cells (HUVECs) isolated from normal pregnancies and cultured for 14 days in the presence of D-glucose concentrations fluctuating between 5 and 20 mmol/L increased the sensitivity to apoptosis compared to cells exposed to normal D-glucose (5 mmol/L) or continuous high D-glucose (20 mmol/L) [93]. Indeed, exposure of HUVECs to intermittent normal and high D-glucose resulted in higher expression and activity of protein kinase C (PKC), higher amount of nitrotyrosine and 8-hydroxy-2′ -deoxyguanosine (8-OHdg, a marker of oxidative stress) [96] and higher expression of p67 phox, p47 phox, and p22 phox NAD(*P*)H oxidase subunits [97]. These findings suggest a role of oxidative stress in HUVECs apoptosis due to fluctuations in the extracellular D-glucose concentration. The role of superoxide dismutase mimetics and mitochondrial respiration are approaches that have also been assayed in HUVECs exposed to intermittent extracellular high D-glucose. The intermittent normal/high D-glucose–associated increase in the level of nitrotyrosine and 8-OHdg, decreased the expression and activity of B-cell lymphoma 2 (Bcl-2, involved in regulation of cell death), and increased caspase-3 expression and activity in these cells was related to ROS overproduction by the mitochondria [98].

Oxidative stress is implicated in the pathogenesis and progression of GDM [6,99,100]. Rapid glucose fluctuations resulting in hypoglycaemia and hyperglycaemia spikes in a 24 h cycle is positively correlated with markers of oxidative stress and inflammatory cytokines in patients with GDM [60,100]. These alterations associate with decreased endothelial cell function as well as adverse pregnancy outcomes [101]. Even when the glucose concentration changes during pregnancy have been monitored throughout the day by CGM [77,102], only few studies

investigated an association of glycaemia and interstitial fluid glucose concentration recordings and oxidative stress in GDM.

Evaluation of the day-to-day glycaemia by *MODD* and *MAGE* in pregnant women with GDM showed higher *MAGE* compared with pregnant women with normal pregnancies [103]. In these patients, higher *MAGE* correlated with lower β-cell function, reduced early-phase insulin secretion, and insulin resistance [103]. Although the levels of oxidative stress markers were not measured it was suggested that oxidative stress might be higher, paralleling a higher *MAGE* supporting the possibility that this metric may help assess the risk of diabetes mellitus-associated complications.

Studies performed in not pregnant women with T1DM show contrasting results. The evaluation of the effects of long-term glycaemia fluctuations on microvascular complications in a cohort of the Diabetes Control and Complications Trial (DCCT) showed no association between the risk of retinopathy and nephropathy and glycaemia dynamic metrics, $\overline{X}$, *SD*, and *MAGE* [104]. The latter is intriguing since retinopathy and nephropathy are diabetes mellitus-derived complications related to increased oxidative stress status. Yet, there was no correlation between increased oxidative stress estimated by measuring 15(*S*)-8-isoPGF2α concentration in urine with *MODD*, *MAGE*, and *CONGA* [105].

Patients with T2DM also show increased production of free radicals, a phenomenon related to hyperglycaemia, insulin resistance, and hyperinsulinemia [106]. Moreover, the association between glycaemic variability and oxidative stress has been studied in these patients [107,108]. In this context, patients with T2DM exposed to oscillations of glucose concentration between 5 and 15 mmol/L (every 6 h for 24 h) associated with more harmful effects than exposure to a constant glycaemia of either 10 or 15 mmol/L (24 h). The results showed reduced flow-mediated dilation, indicative of a higher degree of endothelial dysfunction, and increased nitrotyrosine and free 8-isoPGF2α in plasma, indicative of higher oxidative stress when oscillating glycaemia was applied in these patients [89]. It is also reported that increased levels of nitrotyrosine and free 8-isoPGF2α correlate with *MAGE* in these patients [109]. However, metrics for glycaemia dynamics in T2DM not always associate with the degree of oxidative stress since lack of association between *MAGE* and *MODD* and oxidative stress estimated as 8-isoPGF2α in the urine is also reported in patients with this disease [110].

Other studies show that *MAGE* correlated with the development of coronary artery disease in patients with T2DM who underwent coronary angiography and felt chest pain [111]. It is reported that a history of GDM associates with higher risk of overall and specific cardiovascular diseases [112]. On the other hand, patients that develop GDM with subsequent progression to T2DM were linked with increased risk of cardiovascular diseases [113]. Knowing that cardiovascular disease relates to hyperglycaemia-increased oxidative stress and that oxidative stress is worsened and accelerated by variations in glycaemia dynamics [107,108], disorders of the regulation of plasma glucose concentrations may associate with coronary artery disease in patients with T2DM. However, *MAGE* was not correlated with coronary artery disease, myocardial infarction, cerebral stroke, peripheral artery disease, retinopathy, nephropathy, and peripheral neuropathy in a group of 99 patients with this disease [114]. In the latter study, the patients were subjected to seven measurements of plasma glucose concentration from capillary blood measured 10 min before and 90 min after breakfast, lunch, and dinner, and at 03:00 am. The lack of correlation seen in *MAGE* metrics following a fixed number of glycaemia determinations at specific times with less frequency may not stand for what the CGM data may support for *MAGE* (and other metrics) calculations.

5. Association of glycaemia dynamics with perinatal outcome

Women with GDM having proper integral management of their glycaemia, especially when managed via diet and lifestyle modifications, show a low risk of preeclampsia and primary caesarean delivery, lower offspring birth weight, inadequate gestational weight gain, or incidence of gestational diabesity [7,77,115]. The effectiveness of CGM to reach proper maintenance of maternal glycaemia in accepted ranges and pregnancy outcomes has been scarcely studied (Fig. 5). In a prospective cohort study including 150 Chinese women with GDM [77] subjected to CGM for 72 h, along with *MAGE*, *SD*, $\overline{X}$, and *MOOD,* the maternal outcomes preeclampsia, caesarean delivery, and composite neonatal outcomes were analysed. Interestingly, patients under CGM showed lower *MAGE*, *SD*, and $\overline{X}$ paralleled by lower risk of preeclampsia and primary caesarean delivery compared with women without the CGM approach, indicating also behavioral changes perhaps having a placebo effect due to the close monitoring or the results of more effective treatment adaptations. A lower incidence of preeclampsia was also reported in a group of 139 women with GDM that correlated with CGM-derived metrics [116]. Thus, CGM and antenatal care of women with GDM result in improved approaches to reduce the potential effects of a disrupted glycaemia dynamics in these patients leading to a better pregnancy outcome [77].

Some studies show that CGM metrics in women with GDM not necessarily associate with favourable outcomes, including unaltered caesarean sections rate [117–119], preeclampsia, pregnancy-induced hypertension, and maternal lacerations [118]. It has been proposed that a strict glycaemic control by CGM may not improve fetal outcome compared to SMBG (referred by the authors as a 'liberal glycaemia control') [120]. Furthermore, fetal outcomes are not different in women using CGM compared with the SMBG approach. However, lower *MAGE*, *SD*, and $\overline{X}$ for glycaemia dynamics associated with lower mean neonate birth weight in patients with GDM under CGM approach than patients without this approach [77]. Therefore, CGM may leads to better treatment adjustments to patients with GDM than the SMBG approach in terms of improving maternal and fetal outcomes [121].

CGM could also help pregnant women with pre-pregnancy T1DM since these patients showed higher *%TIR* than pregnant women without this disease [83]. The latter study also showed that neonates to these patients exhibit a lower incidence of large for gestational age, fewer episodes of neonatal hypoglycaemia, a reduced stay of 24 h or more in neonatal intensive care, and a lower number of days requiring a hospital stay. Thus, lower exposure to maternal and subsequent fetal hyperglycaemia is beneficial for better maternal and neonatal outcomes in women with pre-pregnancy diabetes.

One study reported that high fasting plasma glucose in women with GDM associated with higher carotid intima-media thickness and carotid-femoral pulse wave velocity in their 6-years old children [122]. Moreover, children between 4 and 7-years old born to women with normal pregnancies with increased HbA1c level in pregnancy showed altered glycaemia homeostasis, high fasting glucose, and reduced insulin sensitivity [123]. The Hyperglycaemia and Adverse Pregnancy Outcome (HAPO) follow-up Study which included 4160 children aged 10–14 years [124] showed that the offspring to GDM when the mothers were untreated for this disease were insulin resistant with limited β-cell compensation compared with offspring of mothers without GDM. Thus, an adequate glycaemia dynamic is necessary also for a healthy child, and perhaps in the young and adulthood.

6. Final remarks

A clear description of the glycaemia dynamic is crucial and determinant in diseases where glucose handling is altered such as in women with GDM and patients with T1DM and T2DM. According to what is known about the characteristics of the changes in glycaemia in these patients, the protocols for treating them are adapted to their particular conditions. GDM is a disease associated with maternal hyperglycaemia that end in fetal hyperglycaemia [3,4]. This disease of pregnancy is harmful for the mother, fetus, and newborn, and has postnatal consequences such as increased risk of GDM, T2DM, obesity, and

hypertension in young and adulthood [4,6,7]. Unfortunately, few reports address the consequences of an altered glycaemia dynamics on the newborns to GDM.

Monitoring of glycaemia gives an estimate of the changes over time in the blood glucose levels in patients with GDM, T1DM and T2DM. The CGM gives an extensive range of interstitial fluid glucose concentrations considered a close index of glycaemia values [29]. In addition, CGM is considered an approach useful for predicting hyperglycaemia and hypoglycaemia events in patients with diabetes mellitus. The predictive potential of this approach is based on the several parameters that can be derived from a record trace from short (24 h) or longer (several days) periods, including joint data analysis, plane distribution analysis, amplitude, score values, variability estimation, and time series (see Tables 1-6). A summary of the most used analysis derived from CGM and their correlation with related diseases (GDM, T1DM, T2DM, oxidative stress, perinatal outcome, and cardiovascular complications) is given in Table 7. CGM approach in patients with GDM is more sensitive than self-monitoring blood glucose and predictive of insulin requirement in these patients as well as for macrosomia and large for gestational age fetus when reduced *%TIR*. Other studies proposed that *MAGE* is a metric that could be useful for prediction of other diseases of human pregnancy, such as preeclampsia (Fig. 5).

CGM may also unveil mechanisms associated with the effectiveness of insulin therapy on the regulation of glucose concentration in the blood in women with GDM. It has been proposed that insulin therapy along with reducing the plasma glucose concentration in women with GDM to values in a physiological range during pregnancy and at delivery may also alter the metabolism of the mother, placenta, and fetus. Thus, insulin therapy in women with GDM may result in higher risk of hypertensive disorder of pregnancy and supraphysiological gestational weight gain in the mother, impaired placental insulin signalling, and higher mother-*to*-fetus D-glucose transfer, higher endothelial L-arginine/NO signalling, and reduced birth weight [6,7,12,80]. Insulin therapy is also associated with higher risk of developing non-communicable adult diseases including hypertension, obesity, T2DM, and GDM. Whether specific metrics associated with glycaemia dynamics are useful in predicting the alterations caused by insulin therapy in the mother, fetus, and newborn, is not yet reported. Women with GDM are usually

Table 7
Correlation of most used CGM metrics with functional alterations in patients with diabetes mellitus.

Metric	Advantages	Disadvantages	Disease	Correlation	Alteration or observation	References
$\overline{X}$	Most commonly used Helpful in comparing between patients Useful for monitoring patient's disease progress Easy to calculate	It is highly perturbed by outlier values Outlier values are also referred to as *High* or *Low*, creating ambiguity in the calculation of this parameter	T2DM	Negative	Flow-mediated dilation	[88]
			T2DM	Positive	Carotid intima-media thickness	[88]
			GDM	Positive	Mean birth weight	[77]
SD	Most common metric to evaluate glycaemic variability Easy to calculate	Metric highly perturbed by outlier values Users may not know how this metric is calculated Users may be unclear on the meaning of this metric	T2DM	Positive	Coronary plaque vulnerability	[87]
			T2DM	Positive	Risk of coronary artery disease	[87]
			T2DM	Positive	Vascular endothelial dysfunction	[90]
			GDM	Positive	Mean neonate birth weight	[77]
%TIR	Simple to measure Highly sensitive to clinical interventions	Subjected to the arbitrariness of the target range selected by the treating professional The selected range may not be optimal to consider in analyzing the glycaemia variations in a patient	T2DM	Negative	Vascular endothelial dysfunction	[90]
			T1DM	Negative	Risk of LGA in 2nd and 3rd trimester of pregnancy	[139]
			T1DM	Positive	Macrosomia Shoulder dystocia Neonatal hypoglycaemia NICU admission >24 h	[139]
MAGE	Useful to describe major glycaemia fluctuations in postprandial peaks Directly proportional to and highly correlated with SD giving an estimation of glycaemia variability	Statistically is less efficient to estimate glycaemia variability than SD A peak in this metric defines excursion amplitude exceeding an arbitrary level of 1 SD Uncertain which value of SD must be used when calculating MAGE with SD variations in a multiday or multiweek glucose time series	T2DM	Positive	Coronary plaque vulnerability	[87]
			T2DM	Positive	Risk of coronary artery disease	[87]
			T2DM	Positive	Level of C reactive protein	[41]
			T2DM	Positive	Insulin resistance	[111]
			T2DM	Negative	Endothelium-dependent dilation of brachial artery	[41]
			T2DM	Positive	Levels of nitrotyrosine and 8-iso-PGF2α	[109]
			T2DM	Positive	Vascular endothelial dysfunction	[90]
			GDM	Negative	Pancreas β-cell function	[103]
			GDM	Negative	Early-phase insulin secretion	[103]
			GDM	Positive	Mean neonate birth weight	[77]
MODD	Proportional to *SD* High correlation with *SD* Easy to calculate	Defined by two values of glycaemia in consecutive days Assume that the patient had similar meals, activities, and therapy on both days of measurement	T2DM	Positive	Coronary plaque vulnerability	[87]
			T2DM	Positive	Risk of coronary artery disease	[87]
			T2DM	Positive	Level of C reactive protein	[41]
			T2DM	Negative	Endothelium-dependent dilation of brachial artery	[41]
			T2DM	Positive	Insulin resistance	[41]

$\overline{X}$, sample mean; *SD*, standard deviation; *%TIR*, time in range; *MAGE*, mean amplitude of glucose excursion; *MODD*, mean of daily differences; T2DM, type 2 diabetes mellitus; GDM, gestational diabetes mellitus; LGA, large-for-gestational age; NICU, neonatal intensive care unit; 8-iso-PGF2α, 15(S)-8-iso-prostaglandin-F2alpha. For general information about advantages and disadvantages see [48] and [138].

considered as a general group despite the pre-pregnancy maternal BMI (i.e. normal weight, overweight, obese). The consensus is to apply a common therapy to these three groups of women with GDM, including a change in the lifestyle, controlled healthy diet, exercise, oral administration of hypoglycaemic agents, or insulin therapy. However, women with gestational diabesity are a group of patients carrying metabolic alterations that are different from lean and perhaps overweight women that develop GDM [6,7,19–21,77,115]. Therefore, it would be crucial to have a clearer and specific set of metrics derived from glycaemia dynamics in women with GDM lean, GDM overweight, and gestational diabesity. Unfortunately, there is no information addressing the different metrics for glycaemia dynamics derived from the CGM approach in pregnant women separated by pre-pregnancy BMI. In an early study, CGM was applied to a pool of women with GDM treated with diet and insulin, showing pre-pregnancy BMI in the range of overweight and obesity (BMI 30.1 ± 5.1 kg/m^2) [78]. The metrics derived from the data collected from these patients ($\bar{X}$ for 24-h glycaemia, mean glucose level during the night, *AUC*, and *TIR*) were unaltered compared with women with GDM under diet or those referred to as having normal pregnancies. Unfortunately, the groups used for this comparison included women with pre-pregnancy BMI 25.0 ± 5.61 kg/m^2, i.e. a mix of normal weight plus overweight, and 27.2 ± 6.31 kg/m^2, i.e. a mix of overweight plus obese, respectively. Thus, whether the lack of differences in CGM metrics described in this study was because including in the same group women with GDM with pre-pregnancy overweight and obesity is unclear. Thus, the potential importance of separating the study groups as per their pre-pregnancy BMIs or adiposity is critical regarding the interpretation of glycaemia dynamics as a tool for a better characterization of patients. Furthermore, along with GDM lean and gestational diabesity, the intermedium group of women with pre-pregnancy overweight are still in the shadows about the specific alterations that GDM may cause for the mother, the fetus, newborn, and the health of the young and adulthood.

Glycaemia dynamics are a useful tool as a potential predictor set of metrics for complications of pregnancy including GDM and pre-eclampsia. Indeed, the predictive value of glycaemia dynamics metrics might be different for at least these two diseases of pregnancy. We hypothesize that a better understanding of glycaemia dynamics as earlier as possible in pregnancy, and even before getting pregnant, will allow a better therapeutic control of the pregnant women with diagnose of GDM (Fig. 6). The early identification of a metric or a mix of metrics derived from glycaemia dynamics pattern in pregnant women may help to reduce an adverse pregnancy outcome. We also emphasize the need for having a clearly defined pattern of glycaemia dynamics in pregnant women with pre-pregnancy normal weight, overweight or obesity before the diagnosis of GDM. A screening of the several metrics derived from the CGM approach (see Tables 1-6) will allow configuring prevention measures for the development of GDM and other diseases of pregnancy. Also, further and decided deep analysis of the glycaemia dynamics metrics in pregnant women with and without earlier records of GDM or preeclampsia is needed. A detailed analysis may help patients care and protect the health of the growing fetus, the newborn, and young and adulthood.

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CRediT authorship contribution statement

Paola Valero: Conceptualization, Methodology, Investigation,

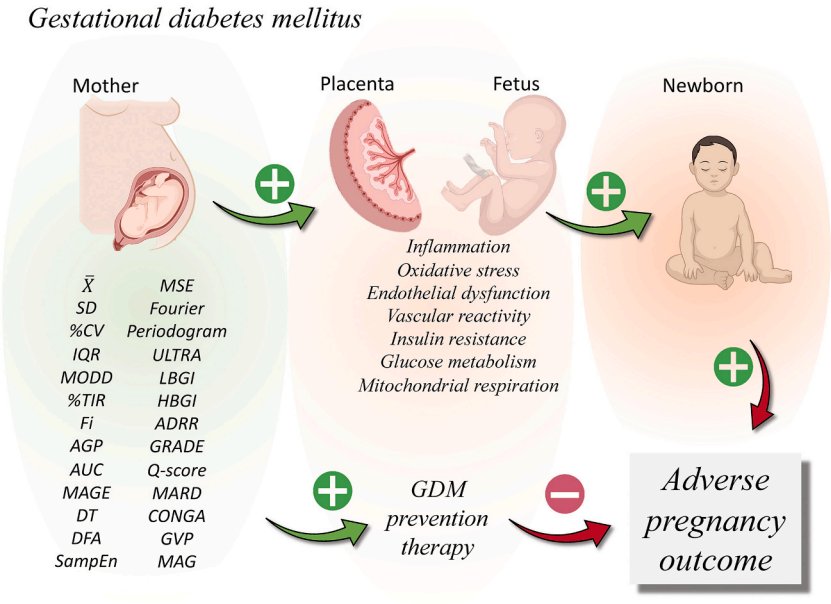

Fig. 6. Proposal for reducing the impact of the interstitial fluid glucose dynamics in gestational diabetes mellitus. Women that get pregnant may develop gestational diabetes mellitus (*Gestational diabetes mellitus*) causing alterations (green arrow and green plus circle) in the structure and function of the placenta and fetus. Changes in pregnancy impact negatively (red arrow) the newborn leading to an adverse pregnancy outcome. When the several metrics of the interstitial fluid glucose concentration (see Tables for details) are measured early in pregnancy (i.e. before diagnose of gestational diabetes mellitus), the interpretation of these metrics in terms of glycaemia management in women with gestational diabetes mellitus may help to generate a protocol for prevention of this disease (*GDM prevention therapy*). The latter is proposed as a way to reduce the effect of the disease on the placenta, fetus, and newborn reducing the risk of abnormal pregnancy outcome. GDM, gestational diabetes mellitus. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Writing – original draft, Writing – review & editing, Visualization. **Rodrigo Salas:** Methodology, Writing – review & editing. **Fabián Pardo:** Investigation, Writing – original draft. **Marcelo Cornejo:** Investigation. **Gonzalo Fuentes:** Investigation. **Sofía Vega:** Investigation, Writing – original draft. **Adriana Grismaldo:** Investigation, Writing – original draft. **Jan-Luuk Hillebrands:** Writing – review & editing. **Eline M. van der Beek:** Writing – review & editing. **Harry van Goor:** Writing – review & editing. **Luis Sobrevia:** Conceptualization, Methodology, Investigation, Writing – original draft, Writing – review & editing, Visualization, Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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