Seventy two-hour glucose monitoring profiles in mild gestational diabetes mellitus: differences from healthy pregnancies and influence of diet counseling

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Abstract

Objective: To study glucose profiles of gestational diabetes (GDM) patients with 72 h of continuous glucose monitoring (CGM) either before (GDM1) or after (GDM2) dietary counseling, comparing them with nondiabetic (NDM) controls.

Design and methods: We performed CGM on 22 GDM patients; 11 before and 11 after dietary counseling and compared them to 11 healthy controls. Several physiological and clinical characteristics of the glucose profiles were compared across the groups, including comparisons for pooled 24-h measures and hourly median values, summary measures representing glucose exposure (area under the median curves) and variability (amplitude, standard deviation, interquartile range), and time points related to meals.

Results: Most women (81.8%) in the GDM groups had fasting glucose <95 mg/dL, suggesting mild GDM. Variability, glucose levels 1 and 2 h after breakfast and dinner, peak values after dinner and glucose levels between breakfast and lunch, were all significantly higher in GDM1 than NDM ($P < 0.05$ for all comparisons). The GDM2 results were similar to NDM in all aforementioned comparisons ($P > 0.05$). Both GDM groups spent more time with glucose levels above 140 mg/dL when compared with the NDM group. No differences among the groups were found for: pooled measurements and hourly comparisons, exposure, nocturnal, fasting, between lunch and dinner and before meals, as well as after lunch ($P > 0.05$ for all).

Conclusion: The main differences between the mild GDM1 group and healthy controls were related to glucose variability and excursions above 140 mg/dL, while glucose exposure was similar. Glucose levels after breakfast and dinner also discerned the GDM1 group. Dietary counseling was able to keep glucose levels to those of healthy patients.

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Introduction

Diabetes during pregnancy is associated with fetal macrosomia, stillbirth, neonatal metabolic disturbances and related problems (1). There is increasing evidence that the intrauterine environment affects the fetal metabolic

programming and that either an excess or a deprivation of nutrients predisposes obesity and metabolic diseases later in life, including diabetes mellitus (2). It has been demonstrated that treatment for gestational diabetes

mellitus (GDM) reduces the risks of serious perinatal morbidities (3, 4), although there is a lack of agreement on both the diagnostic criteria and the metabolic aims to the management of GDM patients.

Historically, the treatment for pregnancies complicated by diabetes has been to maintain blood glucose as close to normal as possible. Furthermore, it was demonstrated by Hernandez *et al.* (5) that current blood glucose targets, recommended for GDM pregnancies, were above those observed in normal pregnancies. However, a randomized controlled trial has never compared current glucose targets vs lower glucose targets powered on maternal and fetal outcomes. The Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study was designed to clarify the associations of maternal glucose levels at thresholds lower than those observed in GDM diagnoses via 75 g 2-h oral glucose tolerance tests (OGTTs) and their corresponding perinatal outcomes. A strong continuous association between increasing glucose levels and perinatal outcomes was identified, although no obvious threshold at which the risks increased could be identified (1). Based on the results of this study, the International Association of the Diabetes and Pregnancy Study Group (IADPSG) suggested new diagnostic criteria for GDM with lower glycemic thresholds (6). Therefore, GDM has become an even more prevalent condition, and patients present less intense metabolic disturbances according to the new diagnostic criteria. It is of great clinical interest to understand further the glucose profiles of this “new group” of GDM patients, comparing them to normal pregnancies.

Continuous glucose monitoring (CGM) enables us to study glucose profiles in detail, helping to unmask differences otherwise not detected by the self-monitoring of blood glucose by fingerstick glucose determinations. The objective of this study was to assess glucose profiles with the 72-h CGM of GDM patients in the second half of their pregnancies, in order to compare them with healthy controls for pooled 24-h measures and hourly median values, summary measures representing glucose exposure (area under the median curves) and variability (amplitude, standard deviation, interquartile range), and time points related to meals either with diets *ad libitum* or after dietary counseling.

Methods

Subjects and methods

Fifty women were included in this study. Thirty-six GDM pregnant women, according to IADPSG criteria (6), were

consecutively recruited for this study from July 2012 to September 2013, from prenatal diabetes care units in two hospitals in Belo Horizonte, Brazil ('Hospital das Clínicas da Universidade Federal de Minas Gerais' and 'Santa Casa de Belo Horizonte') during their first routine visit after receiving OGTT test results. Another 14 healthy pregnant women from the same institutions, matched by prepregnancy BMI, were recruited as controls. They were all 18–42 years old, and between the 24 and 36th weeks of singleton pregnancy. The OGTTs were performed between 24 and 28 weeks' gestation and the CGMs were performed between 27 and 36 weeks' gestation, as pregnant women usually delay to return to appointment in our system (Table 1). The study protocol was approved by both local institutional ethics committees, and after being informed about the study protocol, all the women signed to voluntarily participate.

Exclusion criteria included diseases or drug use that affect glucose metabolism, history of GDM or macrosomic fetus in previous pregnancies, overt diabetes as defined by fasting glucose ≥ 126 mg/dL or HbA1c $\geq 6.5\%$, need of insulin therapy, tobacco use, poor compliance to study protocol, including poor adherence to dietary recommendations or CGM procedures.

From the initial 50 women, 33 completed the 72-h CGM study, after excluding 10 due to CGM procedural errors or incomplete exams, 2 who needed insulin therapy, 2 who did not adhere to dietary recommendations and 3 who voluntarily withdrew from the study. Twenty-two pregnant women who had at least one of the following:

Table 1 Characteristics of the study population.

	GDM1 (n = 11)	GDM2 (n = 11)	NDM (n = 11)
Age (years)*	32 (6)	34 (6)	30 (6)
Prepregnancy BMI (kg/m ²)*	26 (5)	25 (5)	24 (3)
Weight gain (kg)*	9 (4)	7 (3)	9 (3)
Parity [#]	1 (0–2)	1 (0–1)	1 (0–2)
Gestational age at OGTT (weeks) [#]	25 (25–28)	25 (25–27)	26 (24–27)
OGTT fasting (mg/dL)*	87 (10) [#]	85 (8)	76 (7)
OGTT 2 h (mg/dL)*	178 (21) ^{##}	161 (11) ^{##}	100 (24)
Gestational age at CGMS (weeks) [#]	32 (31–35)	32 (30–35)	31 (30–32)
Gestational age at delivery (weeks) [#]	38 (38–39)	39 (38–39)	40 (39–40)

Data are *mean (s.d.) or [#]median (lower, upper quartile) according to normality distribution tested by Shapiro–Wilk. Comparisons using ANOVA or Kruskal–Wallis. BMI, body mass index; CGMS, continuous glucose monitoring system; OGTT, oral glucose tolerance test. [#] $P < 0.05$ vs NDM; ^{##} $P < 0.001$ vs NDM. All other P values for comparisons of the GDM1 and GDM2 groups with the NDM group were nonsignificant.

Figure 1

Enrollment and group formation.

fasting glucose ≥ 92 mg/dL, 1 h ≥ 180 mg/dL and 2 h ≥ 153 mg/dL were allocated to the GDM group (6). The remaining 11 pregnant women composed the nondiabetic group (NDM), as shown in Fig. 1.

Complete interstitial glucose profiles were measured in the 33 women for 72 h using the continuous glucose monitoring system (CGMS) Gold (Medtronic MiniMed, Symlar, CA, USA), between their 27th and 36th weeks of pregnancy. The sensor was inserted into the lumbar region, and the CGMS calibrated four times per day against fingerstick determinations, as per manufacturer's guidelines. Identical glucometers were provided by the investigators (Accu-Check Performa, Roche Diagnóstica), and their accuracy was checked at the beginning, in the middle and at the end of the study. A deviation of 10% compared with certificated laboratory measures was accepted. The patients were instructed to code their time of food intake into the monitor at the beginning of the meal. The NDM group and 11 women from the GDM group, who were randomly assigned to the GDM1 group, underwent the CGM immediately after inclusion, with recommendations to keep their usual pattern of food intake. The remaining 11 women of the GDM group (GDM2 group) received supervised dietary counseling in accordance with the institution protocol (30–35 kcal/kg body weight, 40% carbohydrate, 25% protein, 35% fat) and underwent the CGM after 2 weeks of confirmed compliance to dietary recommendations. During the 3-day CGM, they all registered their food intakes and, through these records, we could ensure that the women of the GDM1 group ingested high amounts of simple

carbohydrates as opposed to those from the GDM2 group, who showed compliance to dietary counseling.

CGM data

Pregnancy-relevant CGMS-derived glucose variables were chosen as addressed previously by others (7, 8). Due to the specificities of CGM data, we chose either appropriate statistical methods for repeated measurements from the same patient or summary measures, as published elsewhere (9). First, we performed a comparative analysis of pooled glucose measurements reflecting overall average of all values among groups as well as the hourly median glucose value of each group, in order to differentiate the groups in terms of absolute values. Secondly, summary measures were chosen to represent both glucose exposure and variability. Thirdly, we compared the groups for specific glucose time points and percentages of time spent within predefined ranges.

The procedure to construct one summary measure per patient was as follows: CGMS records measures every 5 min, providing 12 data points per hour, thus reaching 36 data points per hour per patient for the whole 72-h period (12 data points vs 3 days). These 36 measures were organized into frequency percentiles, so that each woman had one value representing the 25th, another value representing the 50th and a last value representing 75th percentiles of each hour out of the 24 h.

The area under the median (50th percentile) curve (AUC), as calculated by the trapezoid method for each patient, was used to represent glucose exposure (8), which is important because it represents potential fetal glucose exposure and consequent insulin secretion, which is, in turn, a growth factor (7).

The average difference between the maximum and minimum measures shows the amplitude, while the difference between the 75th and 25th percentiles represents the interquartile range (IQR). Both amplitude and IQR represent glucose variability, which was also assessed by the hourly standard deviation (s.d.) average. We used all these three measures to assess variability since there is no consensus on the best way to assess it. Glucose variability is believed to be associated with oxidative stress and inflammation, and may lead to cellular damage with potential consequences to both the mother and the fetus (8).

Specific pregnancy-relevant glucose time points were chosen, as suggested by Hernandez *et al.* (7): fasting glucose (mean of the 6 measures immediately before 06:00 h), nocturnal glucose (mean of measures from

midnight to 06:00h), premeal glucose (mean of three measures immediately before the beginning of each meal) and glucose within 2 h postmeal, including peak value (highest value within 2 h period after meal), time to peak in minutes and 1-h and 2-h glucose values after meals (taken as the mean of three consecutive values for each). We also included glucose between meals, which was the mean of all the values between 2 h after a meal and the next premeal value. For each one of these variables, the patients had three values, one per day, repeated measures. The groups were also compared by the percentages of time spent with glucose levels less than 60 mg/dL, between 60 and 140 mg/dL, and greater than 140 mg/dL.

Statistical analysis

We have prospectively studied the statistical differences among groups in a primary analysis, and sample size was based on similar previous research designs (10, 11). All variables were tested for normality using the Shapiro–Wilk test, and were shown as mean (s.d.) or median (IQR), as appropriate. The maternal and neonatal characteristics of the study group were compared using ANOVA followed by Tukey or Kruskal–Wallis followed by Dunn's, as appropriate. All summary measures (AUC, IQR, s.d. and amplitude), hourly median values and percentages of time spent within the glucose ranges were compared using ANOVA or Kruskal–Wallis, followed by Tukey or Bonferroni respectively. Variables with repeated measures, including pooled glucose values and glucose time points, were compared among groups using the likelihood ratio test and the mixed effect model, followed by Bonferroni correction. Data were analyzed using GraphPad Prism 5.00 version 2.7.1 and Epi Info 6.04 from the public domain. $P < 0.05$ was taken as significant, except for the variables on which Bonferroni correction was applied ($P < 0.05/3 = P < 0.02$, with a denominator of three due to between-group comparisons).

Results

Maternal and neonatal characteristics of the study groups are shown in Table 1. Among the three groups, there were no significant differences in maternal age, prepregnancy body mass index (BMI), gestational weight gain, parity and gestational age at OGTT, CGMS and delivery. Fasting glucose for OGTT was significantly higher in the GDM1 group than the NDM group ($P < 0.05$). Two-hour OGTT values were significantly higher in both GDM1 and

GDM2 groups when compared with NDM ($P < 0.001$). Interestingly, among the 22 diabetic women, 18 (81.8%) had a fasting glucose for OGTT of less than 95 mg/dL.

Glucose record numbers were 9497 in the GDM1 group, 9426 in GDM2 and 9489 in NDM. There were no significant differences among the pool of glucose measurements of the three groups (mean (s.d.): 96 (20) mg/dL, 92 (16) mg/dL, 91 (15) mg/dL, $P > 0.05$). There were also no significant differences in the comparisons of the hourly median values, except at 20:30 where GDM1 glucose values were higher than those of both GDM2 and NDM ($P < 0.05$ for both comparisons).

The areas under the median curves representing glucose exposure were similar among the three groups ($P > 0.05$), as shown in Fig. 2 ($n = 11$ per group). The three measures of glucose variability (amplitude, interquartile range and standard deviation) were all significantly higher in the GDM1 group when compared with the NDM group ($P < 0.02$ for all comparisons). To visualize the differences in glucose variability, Fig. 3 shows the compiled CGMS data of each group ($n = 11$ per group), representing the 25th, 50th (median) and 75th frequency percentiles. The main differences are in the higher measurements, shown in the 75th curve, and in the variability represented by the area between the 25th and 75th curves (IQR).

Glucose measurements with relation to meals, overnight and fasting are shown in Table 2. We observed that the GDM1 group showed higher glucose levels 1 h

Figure 2

Glucose measurements recorded by CGMS in late pregnancy. Median curves of three groups: GDM1 group ($n = 11$), gestational diabetes, before dietary counseling; GDM2 group ($n = 11$), gestational diabetes after dietary counseling; NDM group ($n = 11$), nondiabetic.

Figure 3

Glucose measurements recorded by CGMS in late pregnancy. Frequency percentile curves: 0,25=25th percentile, 0,50=50th percentile (median), 0,75=75th percentile. (A) GDM1 group ($n=11$), gestational diabetes before dietary counseling; (B) GDM2 group ($n=11$), gestational diabetes after dietary counseling; (C) NDM group ($n=11$), nondiabetic.

Table 2 CGMS glucose variables in study groups.

CGMS variables	Groups		
	GDM1	GDM2	NDM
Breakfast			
Preprandial	89 (11)	88 (10)	89 (11)
1-h postprandial	118 (27)*	108 (17)	100 (14)
2-h postprandial	105 (17)*	94 (21)	89 (14)
Peak value	128 (27)	119 (19)	114 (13)
Time to peak (min)	70 (28)*	56 (27)*	33 (21)
Mean glucose between breakfast and lunch	93 (10)*	94 (16)	86 (11)
Lunch			
Preprandial	88 (12)	85 (13)	85 (12)
1-h postprandial	108 (24)	101 (17)	94 (15)
2-h postprandial	103 (23)	96 (16)	92 (16)
Peak value	117 (28)	110 (17)	105 (14)
Time to peak (min)	69 (35)	70 (35)	57 (35)
Mean glucose between lunch and dinner	96 (13)	92 (10)	92 (11)
Dinner			
Preprandial	93 (16)	88 (14)	88 (13)
1-h postprandial	109 (25)*	104 (19)	94 (15)
2-h postprandial	105 (21)*	96 (14)	93 (16)
Peak value	122 (24)*	117 (17)	107 (16)
Time to peak (min)	66 (32)	68 (28)	59 (35)
Mean glucose between dinner and breakfast	92 (12)	88 (9)	91 (12)
Mean 24-h glucose	96 (20)	92 (16)	91 (15)
Mean nocturnal glucose	91 (12)	87 (10)	89 (12)
Mean fasting glucose	88 (10)	86 (12)	89 (12)

Values are mean (s.d.). Time to peak is given in minutes, other variables in mg/dL. *Statistically significant differences compared with NDM group by likelihood ratio test and mixed effect model ($P<0.02$). Peak value: highest glucose value within 2 h of meal start time; time to peak: time from meal start to peak value within 2 h; 1-h postprandial: mean of three consecutive measures 1 h after the meal start time; 2-h postprandial: mean of three consecutive measures 2 h after the meal start time; preprandial: mean of three consecutive measures directly before meal start time; between meals: mean of all measures between 2-h postprandial and preprandial values of the next meal; nocturnal: mean of all measures between 0 and 6 h; fasting: mean of six consecutive values directly before 6 h. GDM1 group, gestational diabetes, free diet; GDM2 group, gestational diabetes after dietary counseling; NDM, nondiabetic.

and 2 h after breakfast when compared with NDM ($P<0.02$ for both comparisons). Interestingly, the GDM2 group was similar to NDM when comparing the same variables. Furthermore, the time to reach the peak was longer in both GDM1 and GDM2 groups when compared with NDM ($P<0.02$ for both comparisons). Other comparisons with relation to breakfast were not significant.

There were no significant differences in the comparisons with relation to lunch. As with dinner, the significant differences were in the 1-h and 2-h postprandial glucose values, which were higher in GDM1 when compared with NDM ($P<0.02$). Higher peak levels were also observed in GDM1 when compared with NDM

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($P < 0.02$). As observed with breakfast, GDM2 was similar to NDM when comparing the same variables.

The average glucose values between breakfast and lunch were higher in GDM1 than NDM ($P < 0.02$), whereas no significant differences were observed in both lunch to dinner and dinner to breakfast.

The percentages of time in which glucose levels were less than 60 mg/dL and between 60 and 140 mg/dL were similar among the three groups ($P > 0.05$) during the entire CGM period. However, when comparing groups for glucose levels greater than 140 mg/dL, GDM1 was the only group, which showed a median percentage of time with such levels of glucose ($P < 0.02$ for both comparisons). Time with levels above 140 mg/dL was, however, only 3.82% of the total monitoring period, representing only 5 out of the 72 h.

Discussion

We have recently faced more stringent diagnostic criteria for GDM, suggested by the IADPSG and endorsed by the American Diabetes Association (ADA), Endocrine Society and World Health Organization (WHO), which include pregnant women with less intense glucose metabolism abnormalities (6, 12, 13, 14). However, current glucose targets for both the diagnosis and treatment of GDM patients still do not have normalized perinatal outcomes (15, 16). By way of the 72-h CGM, we were able to assess glucose profiles during the third trimester of GDM patients, as defined by IADPSG (6), and compare them to those of matched controls. Furthermore, we addressed the role of dietary counseling with regard to glucose profiles after diagnosis. There has been a continuous effort to standardize CGMS data to facilitate comparisons among studies in pregnancies. We had based our choice on previously published studies, which proposed a rational approach of CGMS data (7, 8). However, we recognize that another recent method named 'Functional Data Analysis' could possibly provide a more holistic interpretation of data, and we thus encourage it to future studies using CGMS data (17, 18, 19).

Our data showed that pooled GDM glucose values as well as glucose exposure obtained through CGM were not different from the control subjects. However, we discovered significant differences in variability, as evaluated by different methods. Interestingly, the data analysis showed a greater percentage of time spent with glucose levels higher than 140 mg/dL in the GDM1 group as compared with NDM, according to a higher glucose variability observed in the same group.

Moreover, when patients were on dietary counseling for 2 weeks before CGM, the glucose variability was similar to the control subjects.

The 72-h CGM has been successfully used for glucose studies in clinical practice (20, 21). Indeed, through CGM, it has been shown to be possible to demonstrate, for the first time, that pooled glucose profiles, as well as the AUC of medians reflecting glucose exposure obtained from a group of mild GDM patients on diagnosis, are not significantly different from the controls. Our data show that the main difference among the groups is not due to sustained hyperglycemia with greater glucose exposure but instead is related to a greater variability and levels exceeding 140 mg/dL in the GDM1 group. However, we advise caution since these data are unique, in that we included patients with glucose values slightly exceeding the diagnostic thresholds for GDM. In fact, patients requiring insulin treatment were excluded from this study in order to avoid heterogeneity within a small group of individuals, and 81.8% of enrolled diabetic women had fasting glucose values less than 95 mg/dL.

However, even studying a group of nonobese patients with mild GDM, we discovered differences among groups, especially related to the GDM1 group and its glucose variability. Furthermore, we observed higher postprandial glucose values in the same GDM1 group, although observed values were below the current therapeutic targets. The differences observed by CGM might eventually justify the poor outcomes observed by others in studies of GDM patients with apparent excellent glycemic control throughout pregnancy (22). Thus, our data shed light on the field, by showing that a group of mild gestational diabetes patients with apparently normal pooled glucose values may show a special 'signature' evidenced by altered glucose variability that might affect outcomes, despite an excellent control during pregnancy. Law *et al.* (17) has indeed suggested that the prevalence of large-for-gestational-age infants among clinically 'well-controlled' GDM patients could be due to failure in detecting glucose level variations in these cases.

After 2-week dietary counseling, no differences were observed in CGM glucose variabilities as evaluated by three different methods as well as the higher postprandial glucose values when compared with controls. Although we understand that our study design, recruiting different patients to the CGM1 and CGM2 groups, is not ideal for evaluating changes due to dietary counseling, the disappearance of all statistical differences when

comparing the groups to pregnant control subjects using a relatively small sample reinforces the importance of dietary counseling for glucose control in pregnancy. However, the authors caution that the flattening of glucose variability here observed in the GDM2 group related to dietary counseling might not be enough to favorably affect perinatal outcomes in all patients, due to the importance of other confounders besides glucose, such as obesity, lipids, cytokines, among others (22, 23). Future studies should possibly address these changes in the same patients, before and after dietary counseling, although we recognize that it could limit the patient sample according to the protocol (16).

Studies conducted on groups at high risk of diabetes, such as other mild or subclinical glucose metabolism disorders, have also observed differences in CGM glucose parameters, suggesting that glucose variability and levels above predefined thresholds seem to be the earliest detectable glucose abnormalities within the range of carbohydrate metabolism disorders (24, 25). Interestingly, a recent study by Wang *et al.* (26) demonstrated that women with previous GDM have elevated glycemic variability parameters, observed by CGM 1-year postpartum, even with normal glucose tolerance, as evaluated by the OGTT.

We further suggest that both increased glucose levels and glucose variability denote a common background characterized by insulin resistance, which does not necessarily mean chronic hyperglycemia. It is notable that increased glucose variability has a negative impact on oxidative stress as well as on inflammatory reactions and endothelial dysfunctions (27). It could thus explain why mild OTTG hyperglycemias correlate with adverse perinatal outcomes, as demonstrated by the HAPO study (1), despite similar glucose exposures, as observed in this study. Whether increased glucose variability and higher postprandial peaks could be directly linked to cardiovascular disease in these patients thereafter is an open question (28).

This study also disclosed interesting data related to punctual glucose values, with significant higher postprandial glucose values in the GDM1 group, as compared with NDM, after both breakfast and dinner. Surprisingly, 1-h and 2-h postprandial glucose values in the GDM1 group did not show statistical differences in relation to lunch for the same comparison, which happens to be the most caloric Brazilian meal, whereas breakfast is usually a very light meal. Furthermore, for the analysis between meals, we found higher glucose values in the GDM1 group only during the mornings. We hypothesize that cortisol and other counter-regulatory

hormones could play a role due to dawn phenomenon, thus increasing insulin resistance in GDM patients mostly in the morning, as suggested by others (29). Both diabetic groups showed longer times to reach the peak postprandial values after breakfast when compared with the control group. It could be due to an alteration in first-phase insulin response and insulin resistance, with delayed glucose disposal (30). Furthermore, time to peak glucose values in diabetic women were closer to 1-h postprandial, and it is advised to take this into account to guide fingerstick monitoring when CGM is not available. However, discrepancy in this last result may be expected due to dietary factors among participants (31).

It should be pointed out that our study carries some limitations. First, a higher number of enrolled patients could possibly have disclosed other different time points among groups, as this analysis was performed through a summary point and, therefore, did not consider the whole pool of measurements. Alternatively, this could be obtained by applying Functional Data Analysis (18). Secondly, as aforementioned, the complexity of CGM procedures, as felt by Brazilian pregnant patients, precluded evaluation of the same patients before and after dietary counseling. Thirdly, sadly, there were some missing points in the 1-h OGTT measurements for diabetic-diagnosed patients, although none was missing for the control group (data not shown). These limitations were overcome by stringent inclusion and exclusion criteria, a large volume of CGM measurements provided by each participant and robust statistical methods applied to the data.

In conclusion, this study shows that the main differences between a mild GDM1 group and healthy controls are related to glucose variability and temporary levels above 140mg/dL, while showing that glucose exposure from groups look very much alike, pointing out to 'apparent' similar whole glucose profiles. The GDM1 group is also discerned by some higher glucose levels after meals, although not necessarily related to caloric intake. Dietary counseling seems to be able to keep glucose levels to those of healthy patients.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Author contribution statement

M P C selected patients, analyzed data and wrote the manuscript; M W L analyzed data and wrote the manuscript; G N T N selected patients and compiled data; P A C M selected patients and reviewed the manuscript; R B N selected patients and reviewed the manuscript; K M A B R selected patients and reviewed the manuscript; R A L P A analyzed data and reviewed the manuscript; A I N participated in the study design, patient selection, data analysis and revision of the manuscript; A R O Jr participated in the study design, data analysis and wrote the manuscript.

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