Good Glucose Control in Type 1 Diabetes – What Does it Mean? What's the Role of Continuous Glucose Monitoring?

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Resumo

Introdução: A A1C é considerada o *gold standard* na avaliação do controlo glicémico. Apesar de reflectir a média das glicemias nos últimos 2-3 meses, não fornece informação acerca das flutuações glicémicas. A monitorização contínua da glicose (MCG) permite: avaliar o controlo glicémico nos períodos nocturnos e pós-prandiais; detectar flutuações glicémicas; identificar hipoglicemias assintomáticas; avaliar o efeito da alimentação e exercício no controlo glicémico.

Objectivo: Avaliar o controlo glicémico, através da MCG, em diabéticos tipo 1 com A1C dentro dos objectivos terapêuticos estabelecidos internacionalmente.

Métodos: A MCG foi realizada em 20 doentes, durante um período de 68,0±3,0 horas, utilizando o CGMS®. Considerou-se normoglicemia valores entre 60-160mg/dL. A1C foi determinada com o DCA 2000®. Idade média dos doentes: 21,1±4,7 anos (14-31); A1C média: 6,8±0,3% (6,3-7,2).

Resultados: Os doentes estiveram, em média, em normoglicemia, hiperglicemia e hipoglicemia por 58,8%, 36,1% e 5,1%, respectivamente. A amplitude foi de 258,8±68,5mg/dL (138-360). Oito doentes apresentaram hipoglicemia assintomática e 9 apresentaram episódios de hipoglicemia nocturna; 19 apresentaram hiperglicemia pós-prandial.

Conclusões: O controlo glicémico é melhor avaliado através da variabilidade glicémica, usando MCG, em complemento à A1C. Mesmo em diabéticos com A1C dentro dos objectivos terapêuticos, a MCG está indicada para avaliação do controlo glicémico e das flutuações glicémicas.

Abstract

Background: A1C is the gold standard for assessing glycemic control. Although it reflects the average of glycemia in the last 2-3 months, it doesn't supply information concerning glycemic fluctuations. Continuous glucose monitoring (CGM) allows: assessing glycemic control in nocturnal and postprandial periods; detecting glycemic fluctuations; identifying asymptomatic hypoglycemia; evaluating the effect of feeding and exercise in glycemic control.

Objective: Assessing glucose control, through CGM, in type 1 diabetics with A1C within therapeutic goals established internationally.

Methods: CGM was realized in 20 patients, with an average duration of 68,0±3,0 hours, using CGMS®. It was considered euglycemia, values between 60-160 mg/dL. A1C was measured with DCA 2000®. Patients had an average age of 19,0 ± 2,7 years (14 - 24); average A1C of 6,8 ± 0,3% (6,3-7,2).

Results: In average, the patients were in euglycemia, hyperglycemia and hypoglycemia for 58,8%, 36,1% and 5,1%, respectively. The amplitude was 258,8±68,5mg/dL (138-360). Eight patients presented asymptomatic hypoglycemia episodes and 9 had nocturnal hypoglycemia episodes; 19 presented postprandial hyperglycemia.

Conclusions: Glycemic control is better assessed through glycemic variability, using CGM, associated to A1C. Even in diabetics with values of A1C within therapeutic goals, the CGM is indicated for evaluation of glucose control and glycemic fluctuations.

INTRODUÇÃO

Since publication of the DCCT, A1C is the gold standard on the evaluation of glycemic control; it's used as a risk marker for diabetes related complications [1,2].

The intensive treatment with multiple administrations of insulin, or with an insulin pump, intends to delay the appearance of such complications [3]. Although the capillary glucose testing, just like in A1C, is traditionally used for monitoring and adjustment treatments, they both present important limitations. Neither of them supplies detailed information about glycemic fluctuations or asymptomatic hypoglycemia's [3,4].

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Continuous glucose monitoring measures interstitial glucose. It was verified that in physiological conditions there is a strong correlation between interstitial glucose and glycemia [4]. However, in periods of rapid glycemic fluctuation (during exercise, after meals) and in periods of hypoglycemia, there is less reliability between interstitial glucose and glycemia. There is some data that show that interstitial glucose reflects better the variations of glucose at a cellular level [5].

On the other hand, continuous glucose monitoring allows: 1- to detect glycemic fluctuations, their frequency, amplitude and duration; 2- to evaluate glycemic control during postprandial and night periods (situations where it's not usual to do glycemic self monitoring) [6]; 3- to identify asymptomatic hypoglycemia; 4- to objectify the effect of physical exercise and food on the patients glycemic control [2,7,8].

It has been verified that diabetics with acceptable values of both A1C and preprandial glycemia, present high frequency of asymptomatic hypoglycemia and postprandial hyperglycemia episodes [9]. In the last years, there have been more studies that show that glycemic fluctuations, especially post-

prandial glycemia, increases the oxidative stress, the production of free oxygen radicals, and the formation of atherosclerosis [7,10]. Glucose variability may be as important as A1C in the development of microvascular complications [11,12]. For some patients, the decrease of glycemic variability, even without the decrease of the A1C can represent an improved outcome [2].

PATIENTS AND METHODS

Twenty type 1 diabetic patients, under insulin therapeutic with multiple administrations, with A1C within therapeutic goals established internationally13 (≤7,5% if age ≤19; ≤7% if >19 years (gender, 10 male, 10 female; age, 21,1 ± 4,7 years; duration of diabetes, 7,5 ± 5,9 years; A1C, 6,8 ± 0,3%; body mass index, 22,6 ± 2,9 Kg/m²; mean ± SD) were submitted to CGM using the CGMS® system. The catheter has electrodes impregnated with glucose oxidase, which is introduced into the subcutaneous tissue. The reaction between interstitial fluid glucose and glucose oxidase located on the electrode produces hydrogen peroxide. This reaction converts the interstitial glucose into an electrical current proportional to the glucose concentration at the site of the catheter insertion [5,9,14]. Detection limits go from 40 to 400mg/dL. The device captures records every 10 seconds, whose average is recorded every 5 minutes, allowing a total of 288 records a day, and 864 records during the 72h exam. The patient must register the multiple events (feeding, insulin doses, exercise, and hypoglycemia) in order to facilitate posterior interpretation of the results [6]. The patient must insert 4 records of capillary glycemia for a day to calibrate the device; those measurements must be made in periods of glycemic stability [2].
Values between 60 and 160mg/dL were considered euglycemia.
Only one patient doesn't do carbohydrates counting.
The A1C was determined in all patients with DCA 2000®.

RESULTS

The mean duration of monitoring was of 68,0 ± 3,0 hours, allowing an average of 816 records.
In average, the patients were in euglycemia for 58,8% of the time. The patient who was for the longest time in euglycemia, was it for 83% of the total monitoring time. One patient was it for only 19% of the time. In average, patients were for 36,1% of the total time in hyperglycemia. All patients presented periods of hyperglycemia. The patient who was for the longest time in hyperglycemia was it for about 81% of the total monitoring time. The mean duration of hypoglycemia was of 5,1%. Six patients did not present periods of hypoglycemia, and another was in such a state for 20% of the total monitoring time. The amplitude (measures fluctuation) was, in average, of 258,8 ± 68,5mg/dL. The patient with the least fluctuation presented amplitude of 138mg/dL; two patients recorded the largest fluctuation presented amplitude of 360mg/dL. One should point out that, in this last case, it was obtained the maximum amplitude value which is allow-

ed with the CGMS® (the difference between the maximum and minimal values that the device can measure is 400-40=360mg/dL). Therefore, it is very likely that these patients presented an even bigger glycemic fluctuation (Table I).

Table I - General Results.

Characteristic	Mean ± SD	Min	Max
Monitoring duration (h)	68,0 ± 3,0	59,3	71,2
Number of sensor values	816,4 ± 35,8	712	854
Number of meter values	17,4 ± 4,4	12	30
Time in euglycemia (%)	58,8 ± 19,3	19	83
Time in hyperglycemia (%)	36,2 ± 18,7	6	81
Time in hypoglycemia (%)	5,1 ± 5,7	0	20
Sensor`s amplitude (max–min) (mg/dL)	258,8 ± 68,5	138	360
Sensor`s minimum (mg/dL)	50,4 ± 12,7	40	76
Sensor`s maximum (mg/dL)	309,2 ± 63,2	210	400

Figure 1 represents the monitoring time distribution of each patient regarding hypoglycemia, euglycemia, and hyperglycemia. We should emphasize, positively, patients 3, 4, 11 and 15 with high percentage of time in normoglycemia, with few hypoglycemias; patients 4 and 11 never presented values bellow 60mg/dL during the monitoring time. On the down side, we can consider patients 2, 8, 9, 12 and 19 which presented longer periods of hyperglycemia than periods of euglycemia. Furthermore, these patients (except 12) presented important frequency of hypoglycemias.
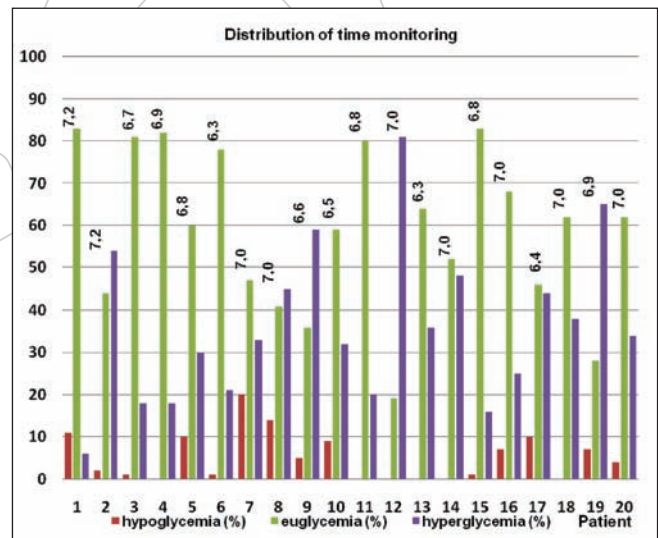

Figure 1 - Distribution of the monitoring time in each patient. On top of the columns is represented the A1C value (%) of each patient.

By analyzing the Figure 2 it is verified that the sensor allows, in almost every patient, to detect higher and lower glycemia values than the glucometer.
By the analysis of Figure 2, it's verified that there are patients with high glycemic fluctuations, mainly patients 2, 7, 8, 16 and 19 (amplitude is measured between the distance between the upper limit of the higher column, and the upper limit of the shorter column).
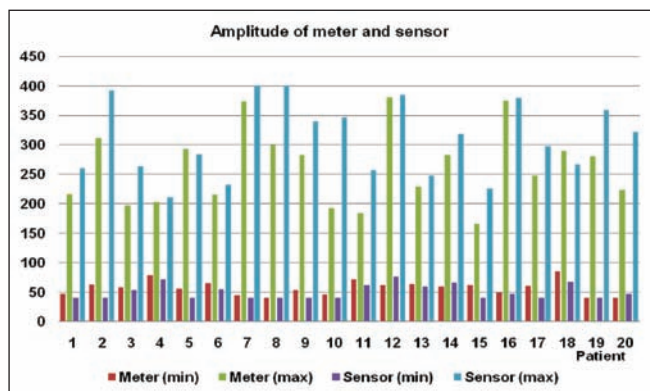
Figure 2 - Comparison between glucose fluctuations detected with glucometer and with the sensor.

Patients 4, 6, 13 and 15 were the ones who presented least glycemic fluctuation.

During the monitoring period, 8 patients presented asymptomatic hypoglycemia and 9 had nocturnal hypoglycemia episodes. The number of nights in hypoglycemia was of 0,8 ± 0,9 nights; 6 patients presented nocturnal hypoglycemia episodes in 2 nights.

Nineteen patients presented postprandial hyperglycemia. In average, it was verified 6,0 ± 2,7 postprandial hyperglycemia episodes. Patient 1 never presented postprandial hyperglycemia episodes; patient 2 presented 11 postprandial hyperglycemia episodes. Despite the big difference between these 2
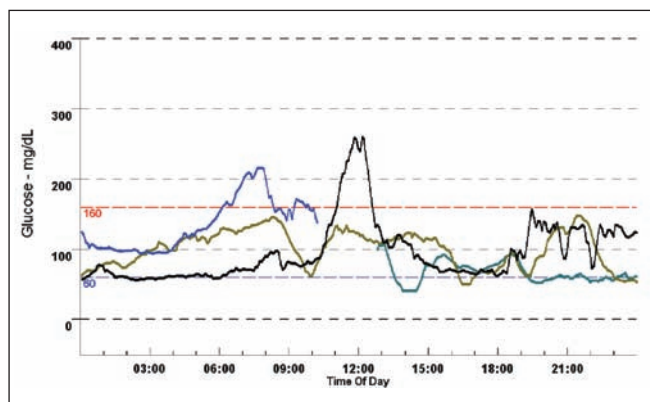

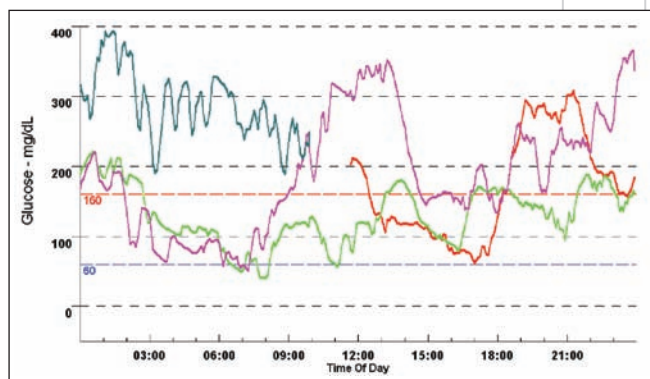**Figure 3 -** Continuous glucose monitoring of patient 1.

Figure 4 - Continuous glucose monitoring of patient 2.
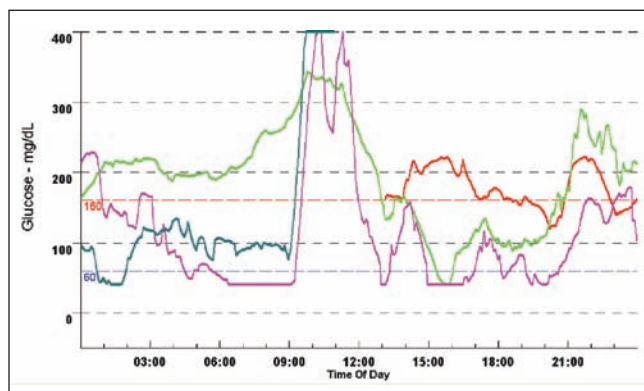

Figure 5 - Continuous glucose monitoring of patient 8.
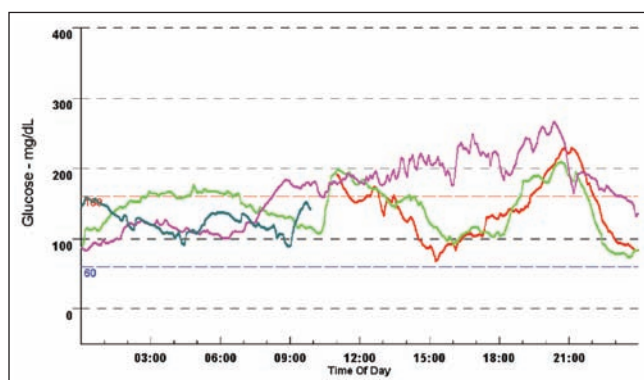

Figure 6 - Continuous glucose monitoring of patient 18.

patients in various aspects (glycemic fluctuations, incidence of postprandial hyperglycemias; Figures 3 and 4), they both presented A1C of 7,2%; the patients 8 and 18 have the same A1C but the glucose control is very different too (Figure 5 and 6). The patients 3-20 presented between 3 and 9 postprandial hyperglycemia episodes during the monitoring time.

CONCLUSIONS

Despite all the studied patients presented A1C within the therapeutic goals, it was verified: 1- high glycemic variability; 2- high frequency of asymptomatic hypoglycemia and nightly hypoglycemia; 3- high frequency of postprandial hyperglycemia.

These results suggest that glycemic control is better evaluated by glycemic variability, through CGM, in complement to the A1C. Patients with the same A1C didn´t have necessarily the same glucose control. Even in type 1 diabetic patients with A1C within the therapeutic objectives, CGM is indicated for the evaluation of glucose control and therapeutic optimization. CGM is a very useful tool on the diabetic's patient education for it allows objectifying the effect of several situations on glycemic control, and thus better guide therapeutic adjustments.

Author Disclosure Statement
No competing financial interests exist.

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