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Original Article

Glycemic variability after high intensity continuous and intermittent exercises in children and adolescents with Type 1 Diabetes

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Abstract
Introduction: Type 1 diabetes mellitus (T1DM) is a chronic disease caused by the immune-mediated destruction of insulin-producing beta cells in the pancreas. Glycemic control is usually monitored by glycosylated hemoglobin concentrations (HbA1c), however, this test has limitations, as you do usually patients with T1DM have high glycemic variability (GV), so including the evaluation of this variable may improve glycemic control. **Purpose:** To assess the glycemic variability and time in range during and after continuous moderate-intensity (MICT) and intermittent high-intensity (HIIT) exercises in children and adolescents with T1DM. **Materials and Methods:** Cross-sectional study included 28 adolescents with T1DM (13.1±1.9 years, duration diabetes 6.4±3.7 years, and HbA1c=9.6±1.5%) submitted to two training sessions, both in a cycle ergometer, with an interval between sessions of at least 48 hours, characterized by a session of MICT and HIIT. The primary outcome was glycemic variation during and in the nine-hour follow-up in both exercise sessions. **Results:** The protocols reduced the mean glycemic variability in period of up to 5 hours after both exercise sessions ($p<0.05$). However, HIIT caused a greater reduction in glycemic variability in the period of two hours after the session compared to MICT ($p=0.01$). There was no significant difference in the meantime in range zone between the HIIT and MICT sessions during the 9-hour follow-up. **Conclusion:** MICT and HIIT produced a reduction in glycemic variation in adolescents with T1DM within 5 hours after the practice of both protocols. The glycemic variability was lower in two hours after the HIIT, suggesting that changes in intensity during exercise are protective in glycemic maintenance after exercise.
Keywords: Glycemic variability; Type 1 Diabetes Mellitus; Physical exercise; Adolescents.

Introduction

Type 1 diabetes mellitus (T1DM) is a chronic disease caused by the immune-mediated destruction of insulin-producing beta cells in the pancreas (Jenkins & Jenks, 2017). Despite improvements in the accuracy of glucose monitors and continuous glucose monitoring systems (CGM), glycemic control during and after physical exercise is still recognized as a major challenge (Yardley, Brockaman & Bracken, 2018).

Exercise is very beneficial for individuals with T1DM, such as known improvements in cardiovascular health, insulin sensitivity and body composition (Chimen et al., 2012). However, fear of hypoglycemia can be a barrier to exercise in this population (Brazeau, Rabasa-Lhoret, Strychar & Mircescu, 2008). Advanced planning is necessary, as these glucose changes during and after physical exercises are quite challenging to manage and enable safe exercise practice. In this sense, individuals with T1DM often fail to comply with exercise guidelines and are less active than their peers without diabetes (Cordella, Teruzzi & Luzi, 2017).

Contradictory results have been reported on the benefits of physical activity in the metabolic control of patients with T1DM, and the most beneficial type of exercise in this group is also controversial (Campaigne, Gilliam, Spencer, Lampman & Schork, 1984; Valerio et al., 2007; Reddy et al., 2019). Some studies have shown that aerobic activities of light to moderate intensity can increase the risk of hypoglycemia after exercise (Mosher, Nash, Perry, LaPerriere & Goldberg, 1998; Campaigne, Gilliam, Spencer, Lampman & Schork, 1984). On the other hand, the inclusion of short sprints of high intensity combined with aerobic exercises of low intensity seems to favor the lower decrease of glycemia after exercises (Valerio et al., 2007; Zinman, Zuniga-Guajardo & Kelly, 1984).

Glycemic control is usually monitored by glycosylated hemoglobin concentrations (HbA1c), as high values of HbA1c are related to a higher risk of microvascular complications (SBD, 2020; Rohlfing et al., 2002). However, this test has limitations, as you do usually patients with T1DM have high glycemic variability (GV), so including the evaluation of this variable may improve glycemic control (SBD, 2020).

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In this way, other accompanying measures are being adopted, such as time on target or time in range (TIR) and the coefficient of variation (CV), both in patients who perform continuous glucose monitoring and also in those who perform various measurements of capillary blood glucose at the same time. Throughout the day, the TIR indicates how long, for a certain period, the patient remained with blood glucose levels between 70 and 180 mg / dL and has a relationship with lower chances of microvascular complications, as it reflects better glycemic control (SBD, 2020).

The maintenance of the CV, with values higher than 36%, is associated with high glycemic variability and a higher risk of hypoglycemia (Monnier et al., 2017). A review study sought to evaluate the post-exercise glycemic response in different types of exercises, suggesting that intermittent training at high-intensity intervals (HIIT) may favor a lower risk of acute hypoglycemia (Lima et al., 2017).

Few studies have evaluated the relationship between TIR and GV during physical exercises. Therefore, the purpose of this study was to assess the GV and TIR during and after continuous moderate-intensity (MICT) and intermittent high intensity (HIIT) exercises in children and adolescents with T1DM.

Materials and Methods

Design of the study

This cross-sectional study evaluated 28 adolescents with T1DM, from the diabetes outpatient clinic of the Pediatric Endocrinology Unit of Curitiba Clinic Hospital of the Federal University of Paraná - UFPR, between (2015 to 2017). The adolescents were invited to participate in the research at the outpatient clinic, where they perform periodic consultations, the participants performed two exercise protocols with an interval of 48 hours between them.

Participants

The sample selection was carried out for convenience. The following were included: Participants diagnosed with T1DM at least 12 months ago; age between 10 and 15 years; Who did not have any diabetes-related comorbidity that would prevent them from exercising; and present a free and informed consent form signed by the legal guardians.

This study was approved by the Human Research Ethics Committee of Curitiba Clinic Hospital - UFPR, CAAE 44193214.7.0000.0096, under opinion number 1.101.60.

Anthropometric assessment

Anthropometric measurements were collected in duplicate using the techniques described by Lohman (1993). Height, measured in centimeters at the end of maximum inspiration, was measured with a portable vertical stadiometer (WCS®, Brazil) to the nearest 0.1 cm. Body mass was measured on a portable digital scale (Filizola®, Brazil), in kilograms (kg).

Blood evaluation

The samples were collected by experienced nurses from the clinic itself. The blood was collected by venipuncture and analyzed by the TurbiClin immunoturbidimetric test (São Paulo - Brazil), to assess HbA1c.

Glucose and insulin monitoring

All participants were instructed to write down their daily insulin dose and record their food intake during the intervention period. The interstitial glucose values were obtained using a CGM (GUARDIAN®RT, Medtronic, Minimed). A CGM sensor was inserted subcutaneously in the patient's lumbar region and collected interstitial glucose measurements every five minutes. The data of glycemic values were analyzed throughout the exercise period and followed up to 9 hours after the protocols.

The data were used to calculate the coefficient of variation (division of the standard deviation from the mean of blood glucose, multiplied by 100) and reflects the GV over a given period. The variability measure is widely used in the assessment of glycemic profiles and demonstrates how much variation or dispersion there is around the average (Hill et al., 2011). The time in the target or TIR was analyzed by determining the time (min) that the patient remained with blood glucose levels between 70 and 180 mg / dL (SBD, 2020).

Nutritional control

During the study intervention period, participants were instructed to record in a food diary all the food eaten, there were no specific guidelines for changes in the nutritional routine of the participants during the period of participation in the study, thus keeping the routine as normal as possible. Quantitative caloric analysis of food intake was performed using the ADS Nutri® diet analysis software, which has a database with more than 3000 registered foods. The Brazilian Food Composition Table was selected as a data source (NEPA, 2006). The pre-exercise meal was standardized individually by a nutritionist, with a portion between 30 and 35% of the daily caloric requirement and of these 50 to 55% was composed of carbohydrates according to the GDR (Table, 2005).

Cardiorespiratory assessment

All subjects visited the laboratory three times with an interval of 48 hours between each visit, the first to perform the cardiorespiratory fitness test ($VO_{2máx}$) using the K4b2® portable gas analyzer using Balke's adapted protocol on a cycle ergometer (Rowland, 1990). The test was started with a load of 25 Watts and a speed of 50 RPM, every three minutes an additional 25 Watts was increased, and so on until the maximum heart rate of the

individual was reached (Tanaka, Monahan & Seals, 2001), or as soon as the individual could not maintain speed and load

Training protocols

After 48 h, the subjects returned to the laboratory to perform the HIIT test, in which the individual pedaled for 30 minutes on a cycle ergometer with a load of 60% of VO_{2max}, with an increase in intensity every 5 minutes, whose increase was called a bout, in which participants were verbally oriented and motivated to pedal at the maximum possible speed for 10 seconds. Therefore, the total of the HIIT protocol consisted of 30 min of moderate activities interspersed with five shots of maximum intensities lasting 10 seconds.

The third visit occurred after 48 hours to perform continuous moderate intensity exercises (MICT), in which each participant remained cycling on a cycle ergometer for 30 min at 60% of $VO_{2máx}$ at a continuous pace.

The insulin therapy used in the intervention days was not altered with average doses of 26.5 ± 7.36 long-acting insulin Glargine (Brazil) and doses of 7.5 ± 3.41 ultra-fast acting insulin Aspart and Lispro (Brazil).

Statistical analysis

Data analysis was performed using the Statistical Package for the Social Sciences (*SPSS*, version 24.0). The results of the quantitative variables were presented using means and standard deviations, while the presentation of the qualitative variables was described by frequencies and percentages. The verification of data normality was performed using the *Shapiro-Wilk* test.

The GV was verified by the CV. Differences between groups at the beginning of the study were verified by Student t test. Differences in glycemic variation during and after interventions by each group and the time per group interaction were verified using the two-way mixed model factorial ANOVA, and when differences were identified, post-hoc Bonferroni was used. The sampling power was calculated posteriorly in the G*Power software (see 3.1.9.2), using the ANOVA test of repeated measures, 15 measures and two groups. Effect size of 0.25, α of 0.05 and a total sample of 28 participants were assigned. According to these parameters, the statistical power was 0.99.

Results

The results of the sample characterization are described in Table 1, a significant difference was observed only for the variable $VO_{2máx}$, between boys and girls, with a higher value for boys (p = 0.001). For the other variables, age, body mass, height and HbA1c, there was no difference between genders.

Table 1. Characterization of the sample.

	Mean (±*SD*)			
	Total	**Girls (n=15)**	**Boys (n=13)**	**p**
Age (years)	13,12 ± 1,97	13,01 ± 2,10	13,25 ± 1,88	0,758
Body mass (kg)	48,59 ± 12,72	50,27 ± 14,06	46,65 ± 11,21	0,463
Height (cm)	123,96 ± 65,85	125,98 ± 65,09	121,62 ± 69,30	0,865
VO_{2max} (ml/kg/min)	37,53 ± 8,26	32,04 ± 5,88	43,87 ± 5,66	**0,001***
HbA1c (%)	9,66 ± 1,57	9,41 ± 1,28	9,95 ± 1,87	0,376

Note: *p<0,05.

The comparison between the MICT and HIIT exercise protocols are shown in table 2, there was a significant difference only in the pre-exercise insulin doses (p = 0.001) and pre-exercise blood glucose (p = 0.001). The glycemic variation during and up to nine hours after exercise, time on target, time on hyperglycemia, time on hypoglycemia, and caloric intake during the intervention days did not show any significant difference between the groups.

Table 2. Comparison of TIR and GV after MICT and HIIT protocols.

	MICT		**HIIT**		
	Mean	***SD***	***Mean***	***SD***	**p**
TIR (min)	194,29	128,77	185,18	164,16	0,818
Time in hyperglycemia (min)	343,75	136,18	344,11	178,32	0,993
Time in hypoglycemia (min)	7,86	27,35	10,71	34,63	0,342
Glycemic Average 30min exercise (mg dL)	199,58	81,59	212,76	79,49	0,543
Glycemic variation 30min exercise (%)	5,25	3,10	6,13	4,88	0,425
Glucose 9h after exercise (mg/dL)	212,17	44,13	209,08	56,48	0,821
Glycemic variation 9h after exercise (%)	26,01	11,69	24,38	10,14	0,578
Caloric intake (kcal/day)	1813,03	551,87	1715,65	475,28	0,133
Pre-exercise insulin dose (U)	6,98	3,72	4,26	3,98	**0,011***
Pre-exercise glucose (U)	339,78	74,24	245,07	101,84	**0,001***

Note. SD: standard deviation; *p<0,05.

The analysis of GV through the CV performed during and up to nine hours after exercise, showed a difference only for the evaluation performed two hours after the end of the exercises, with a lower coefficient for HIIT (p = 0.01). The data are shown in table 3.

Table 3. Comparison between glycemic variations during the 30-minute exercise period and 9 h after practice.

	HIIT			MICT				
	Mean	***SD***	**CV (%)**	***Mean***	***SD***	**CV (%)**	**F**	**p**
5min	199,14	82,52	41,44	214,50	78,85	36,76	0,49	0,49
10min	198,93	83,22	41,83	214,21	80,20	37,44	0,47	0,50
15min	198,57	83,22	41,91	212,57	82,06	38,60	0,39	0,54
20min	199,07	82,16	41,27	213,86	81,87	38,28	0,44	0,51
25min	199,57	81,62	40,90	211,71	80,71	38,12	0,30	0,59
30min	202,21	80,38	39,75	209,71	78,28	37,33	0,12	0,73
1h	225,57	64,90	28,77	194,43	67,14	34,53	3,31	0,08
2h	244,21	58,74	24,05	182,93	56,41	30,84	17,32	**0,01***
3h	228,36	76,22	33,38	205,14	61,86	30,15	1,58	0,22
4h	208,86	69,15	33,11	221,71	79,03	35,64	0,41	0,53
5h	201,64	70,79	35,11	223,86	84,92	37,93	1,10	0,30
6h	195,86	70,81	36,15	217,93	84,55	38,80	1,08	0,30
7h	191,07	75,41	39,47	212,21	83,70	39,44	0,97	0,33
8h	188,29	82,28	43,70	226,29	91,70	40,52	2,70	0,11
9h	191,00	81,49	42,66	222,79	87,05	39,07	2,92	0,09

Note SD: standard deviation; *p<0,05.

The CV curve during and after the exercises is shown in Figure 1. It is observed that for a period of up to 5 hours after the activities, the coefficient of variation remains lower in both exercises, with values below the cutoff value of 36%. Demonstrating less GV during this period.

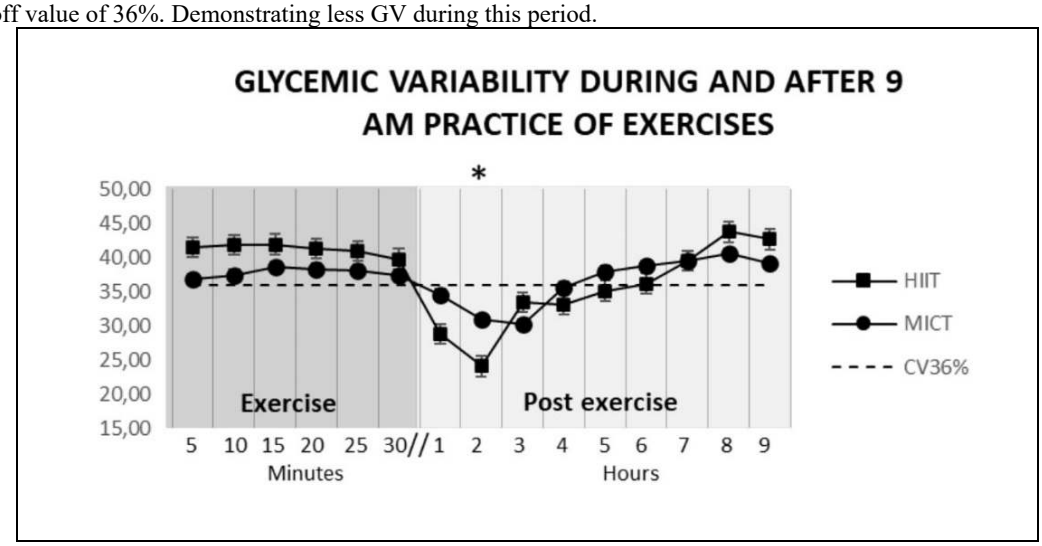

Figure 1. CV curve during exercise.

Discussion

This study aimed to assess GV and TIR during and after continuous and intermittent exercise in children and adolescents with T1DM. The main results indicate less glycemic variability assessed by the variation coefficient in both exercise protocols (MICT and HIIT). This lower variability lasts for a period of up to five hours after the exercises, and only in the two hours after the protocols, HIIT showed less GV about the MICT.

Adequate cardiorespiratory fitness is a health marker in all age groups, including for individuals with T1DM, as VO_{2max} has an inverse correlation with several cardiovascular risk factors such as HbA1c, insulin doses, total cholesterol, LDL, and triglycerides (Vasques, Silva & Lopes, 2007; Austin, Warty, Janosky & Arslanian, 1993). In this study, the VO_{2max} values achieved by T1DM showed lower values for girls compared to boys (p = 0.001). Our results are in agreement with other studies, which demonstrate that during adolescence the performance in VO_{2max} tests tends to be lower for girls than for boys (Rowland et al., 2000; McMurray et al.,

2002; Vasques, Silva & Lopes, 2007), differences associated with growth, maturation phase, and sex hormones that are different between the sexes (Austin, Warty, Janosky & Arslanian, 1993).

In the present study, a significant difference was observed in the pre-exercise insulin doses ($p = 0.001$) and pre-exercise blood glucose ($p = 0.001$) between the MICT and HIIT protocols, with higher values for the HIIT protocol. However, these differences are acceptable because they are related to insulin treatment, in which fast or short-acting prandial insulin is administered before meals or exercises according to capillary blood glucose and the number of carbohydrates to be consumed (Jeitler et al., 2008).

GV was evaluated using the CV performed during and up to nine hours after the exercises. There was a significant difference only in the evaluation performed two hours after the end of the exercise, with a lower coefficient for HIIT ($p = 0.01$). Most of the time, the GV did not show any difference between the protocols of the exercises, which suggests that both forms can be performed safely. In the clinical context, the GV is associated with an increased risk of mortality, both in prospective studies and in randomized clinical trials (SBD, 2020).

One study observed an increase physical activity in adolescents with T1DM and changes in GV, the results showed that although there was an increase in the level of moderate to vigorous physical activity, there was no significant change in glycemic variability (Rebesco et al., 2020). Another study corroborates the present study, demonstrated less glycemic variability after low-intensity physical activities, but the study did not compare it with other exercise protocols (Manohar et al., 2012).

In the present study, during a period of up to 5 hours after the activities, the CV remained at lower levels in both exercises, below the cut-off value of 36%, showing less GV during this period. The two exercise protocols did not differ in response to the GV, so the hypothesis arises that the volume of training has more influence than the type of exercise. A study conducted with type 2 diabetes carriers corroborates this idea because the amount and frequency of physical exercise have proven to be more relevant to glycemic control than intensity and type (Harmer & Elkins et al., 2015).

Our results demonstrated that both HIIT and MICT could acutely assist post-exercise glycemic control, with a lower coefficient of variation. The study corroborates the results found by Cockcroft et al. (2017), who analyzed the effect of acute HIIT exercises and moderate-intensity exercises on the glycemic control of adolescents with T1DM, using continuous glucose monitoring. The results showed that both HIIT and MICT had the potential to improve short-term glycemic control in young people with T1DM.

Blood glucose levels decrease rapidly during activities of light to moderate intensity in individuals with T1DM (Mosher et al., 1998; Campaigne, Gilliam, Spencer, Lampman & Schork, 1984). Some studies have shown that the inclusion of short sprints of discharge activities, alone or combined with aerobic exercises of moderate-intensity, produces lower risk of hypoglycemia during activity and up to 2 h after physical exercise, compared with the aerobic activity of moderate intensity (Valerio et al., 2007; Zinman, Zuniga-Guajardo & Kelly, 1984).

These results corroborate with our study, which showed a significant difference two hours after the end of the exercises with less GV in this period. However, the authors did not verify the variation coefficient analyzed in the present study, which advances knowledge in the area of glycemic control and intensity of acute exercises in individuals with T1DM.

Therefore, it is noteworthy that the strengths of the present study are related to the assessment of blood glucose through the continuous glucose monitor in real-time, with assessments every five minutes, making it possible to analyze the post-exercise glycemic curve. Also, the differential was the assessment of GV by TIR and CV. This study has some limitations, the sample size is reduced and selected for convenience, which can limit the extrapolation of the data, and there was no comparison analysis with a control group.

It is important to encourage children and adolescents with T1DM to exercise regularly, considering the effects of glycemic variability. The present study has shown that there is an influence on the GV evaluated acutely, but that the post-exercise response does not differ between continuous and intermittent exercises. However, future studies are needed to determine the influence of different types of exercise on the coefficient of GV acutely and chronically.

Conclusion

In conclusion, continuous exercises of moderate-intensity and intermittent exercises have similar acute responses in the coefficient of GV of adolescents with T1DM, with less variability up to five hours after exercise. However, glycemic variability was lower in HIIT after two hours of protocol, a factor that suggests that intensity changes during exercise may be protective in glycemic maintenance after practice.

Conflicts of interest

The authors declare they have no conflicts of interest.

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