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Original Article

Physical inactivity is associated with reduced heart rate variability in exercising eutrophic, type 1 diabetic and obese children

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Abstract
Problem Statement: Although there is progress in understanding the impact of obesity and Type 1 diabetes in children, are not fully understood whether these conditions are associated with cardiac autonomic modulation. **Purpose:** To evaluate the effects of the sedentary lifestyle in the HRV of children with DM 1 or obese. **Approach:** After performing the ethical procedures, we applied the International Questionnaire of Physical Activity (IPAQ - C), short version, adapted for children and adolescents. We selected male children aged 6 to 12 years, classified as eutrophic (n = 8), diabetic (n = 8) and / or obese (n = 8). They were then submitted to anthropometric and cardiometabolic evaluations and an aerobic capacity test (Shuttle Run Test). Subsequently, the children were submitted to the 6-minute walk test (6-MWT) to record HRV in response to exercise. **Results**: The parameters of heart rate variability were reduced in DM 1 and obese when compared with eutrophic children (p <0.001). Analysis of heart rate variability in the time domain in the exercise of eutrophic, obese and DM1 children through the cardiac interval, standard deviation, variance and RMSSD were reduced in DM 1 and obese when compared to eutrophic children (p <0.001). The components of low and high frequency by the frequency domain at exercise were reduced in DM1 and obese when compared with eutrophic children (p <0.001). We found positive and significant moderate to very strong correlations between IPAQ and HRV parameters. We also observed moderate to strong correlation between obesity evaluated by Z-score and HRV. There was not correlations between glycemic control infer by Hb1Ac and HRV data. In addition, a very strong association was found between the IPAQ parameters and the cardiac vagal tone assessed by the RMSSD (p <0.0001). **Conclusion**: The level of physical activity showed a strong association with HRV, with lower levels in the obese and DM 1 group.
Keywords: Childhood; Sedentary lifestyle; autonomic modulation; exercise; metabolic control

Introduction

The analysis of heart rate variability (HRV) allows inferring the modulation of autonomic nervous system (ANS) responses in a noninvasive way (1). The analysis of this variability has become of great interest because of its ease and its potential clinical use. In fact, the decrease in HRV is a strong predictor of mortality following acute myocardial infarction (4). By analyzing the spectral density of HRV, it is possible to access how the variation distributes in different frequency bands. These bands are determined by the modulation of the sympathetic and parasympathetic branches of the ANS. Changes in the HRV patterns of children and adults provide a sensitive and early indication of impairment of cardiovascular regulation. Low HRV may be an indicator of inadequate adaptation of the autonomic nervous system in response to physiological stress, such as physical exertion (32).

The physical exercise-induced increase in the demand of contracting muscles for oxygen and substrates represents a challenge for cardiovascular homeostasis and encompasses coordinated responses to match the higher metabolic demands, such as increases in heart rate (HR) and blood pressure. These responses are mediated by afferent signals of baroreceptors, chemoreceptors, and arterial proprioceptors and efferent branches of ANS (33). Normal autonomic adaptation to acute exercise is impaired by several chronic diseases, including

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obesity and diabetes. Thus, the impacts of the metabolic chronic dysfunctions will be more evident by submitting the people to exercise effort.

Obesity induces metabolic and endocrine disorders that may leave the body more susceptible to chronic diseases (22) and at least part of this high risk can be attributed to changes in the ANS. In this sense, obese children present harmful changes in ANS when compared to eutrophic children in resting situations (35; 39). Additionally, Kaufman et al. (22), showed that changes in HRV (high HF: LF ratio and reduced HF) in obese children are dependent on the amount of fat mass and other factors associated with body fat.

Changes in ANS are also present in patients with type 1 diabetes mellitus (DM 1). Chronic hyperglycemic status may promote changes in the afferent branches of the cardiovascular system, impairing baroreflex control and resulting in changes in chronotropic and inotropic response (3). As in obese children, the amount of body mass seems to be a factor that influences HRV in children with DM 1. In this sense, Cho et al. (9) showed that BMI and central adiposity, verified by waist circumference, are associated with dysfunction of ANS assessed by HRV in children and adolescents DM 1, even after adjustment for the control effect glycemic and insulin dose for body weight.

Another aspect that seems to influence the ANS modulation is the level of physical activity. The association of low levels of physical activity with reduced HRV has been demonstrated in obese children (10), with DM 1 (8) and eutrophic (19). Although there is progress in understanding the impact of obesity, DM 1 and physical activity level on children's, the determinants of HRV modulation are not fully understood. To further this issue, in the present study the physical exercise was used to evaluate the association of variables related to obesity, DM 1 and physical activity level with HRV parameters in obese, DM 1 and eutrophic children.

Materials and Methods

Subjects

For this interventional trial, 24 children aged 6-12 years volunteered to participate in the study. All experimental procedures were approved by the Ethics Committee of the Instituto de Ensino e Pesquisa da Santa Casa de Belo Horizonte and were performed in accordance with their policies (nº: CAAE 57120516.6.0000.5138). Parents or guardians of children provided the written informed consent. Children who met the following criteria were included in the present study: age below than 12 years; physically inactive for at least 3 months before initiation of the study. Exclusion criteria adopted were as follows: any complication caused by diabetes or another condition that restricted exercise training.

Experimental design

First, all children completed the International Questionnaire on Physical Activity (IPAQ - C), short version, adapted for children and adolescents. After the questionnaire was applied, the children's medical records were analyzed so that they were classified as eutrophic, diabetic and/or obese. After these preliminary analyses, the children were subjected to anthropometric and cardiometabolic assessments and then, were subjected to aerobic capacity test (Shuttle Run Test). During the second visit, children were subjected to the 6-minute walk test (6-MWT) to record the HRV in response to exercise.

Anthropometric assessment

Body mass was measured using a calibrated analog scale (WELMY, SÃO PAULO, BRAZIL) with 0.1 kg. Height was assessed using a stadiometer with precision of 0.5 cm. The skinfolds were measured using the skinfold caliper (CESCORF, SÃO PAULO, BRAZIL) at triceps (TR) and subscapular (SE) sites with a measurement field between 1 and 65 mm and accuracy of 1 mm. All anthropometric measurements were performed by the same trained evaluator. Using the skinfold thickness values, corporal density was calculated using an equation (5) where % fat = 1,35 (TR + SE) - 0,012 $(TR + SE)^2$ - 4,4). The body mass index (BMI) was calculated and the cut-off points of BMI were those recommended by the WHO (40) (11), which classify the adiposity level according to z-score age-dependent. The nutritional status of the child was categorized as sharpness and thinness (<z-score -3), eutrophic (> -2 and < +1), overweight (> +1 and < +2), obesity (> +2 and < +3) and severe obesity (> +3). (40). The abdominal perimeter (PAB) was measured using a tape measure (CESCORF 2 M, SÃO PAULO, BRAZIL). The PAB was obtained in the lowest localized curvature between the ribs and the iliac crest without compressing the tissues. Cut-off data points were used as recommended by WHO. (41).4 Cardiometabolic parameters

Arterial blood pressure was evaluated by sphygmomanometer model DS44 (Welch Allyn®/Tycos, N.Y, EUA). This procedure was conducted by the same experienced evaluator who admitted the exact moment of early sound (phase I – Korotkoff) and the end of sounds (phase V – Korotkoff) and admitted as systolic arterial pressure (SAP) and diastolic arterial pressure (DAP) values, respectively. Resting heart rate was obtained by a Heart Rate Monitor (POLAR FT 7, Finland). The values of glycated hemoglobin were obtained through the medical records of obese children and with DM1

Assessments of aerobic performance

The maximum aerobic velocity (m/min) was measured using the Shuttle Run (SR) test. Prior start of the test, the children were familiarized with the procedures. The test consisted of a 20-meter run at a rate determined by a beep, until the children could not maintain the pre-determined intensity (24;13). The children used a cardiofrequencymeter to obtain the maximum heart rate (HR_{max}), considered the highest value during the test. The stages of the test were recorded as number of trips throughout the execution. The number of complete stages was compared with a reference table (13).

Spectral analysis of heart rate variability

The heart rate signal was obtained by the Heart Rate Monitor (V800 Polar, USA) The R waves of heart electrical were identified beat by beat, and the pulse interval was computed as the interval between two consecutive beats using a software (Kubios HRV Standart for Windows3.0.2). Time- and frequency-domain analyses were evaluated in exercising children using a 6-min period; period selected from continuous recording during the low intensity exercise. Fast Fourier transformation and Hanning windows (512) with 50% overlap obtained the power spectral density. The spectral power for very low frequency (VLF < 0.04 Hz), low frequency (LF = 0.04–0.15 Hz) and high frequency (HF = 0.15–0.4 Hz) bands were evaluated. To assess the sympatho-vagal balance to the heart, LF/HF ratio of cardiac interval variability was calculated. These bandwidths were previously used to analyze the spectrum of the HR variability in children (38). The integration of power spectrum density within each frequency bandwidth was obtained with the aid of a software (Cardioseries v.2.2, São Paulo, SP, Brazil).

Exercise test to obtain the cardiac intervals

Cardiac intervals used in spectral analysis of HRV were obtained during an aerobic submaximal test. Children were instructed to walk at their maximal speed during the 6 minutes of the test while they received standardized verbal encouragement during the first minute. The distance walked during the 6-MWT was measured with 1-m precision and the test was performed in a standardized hall with a length of 30 m (14).

Statistical Analysis

The data are expressed as the means ± SEM. The Shapiro-Wilk test was used to verify the data distribution. The physical activity, anthropometric, cardiometabolic and heart rate variability parameters were compared using ANOVA one way. The correlations between the physical activity level or Z-score or glicated hemoglobin with heart rate variability parameters were assessed using Pearson's coefficient. These correlations were classified according to Evans's criteria, as follows: 0.00–0.19, very weak; 0.20–0.39, weak; 0.40–0.59, moderate; 0.60–0.79, strong; and >0.80, very strong [41]. The level of significance was set at $p < 0.05$.

Results

The anthropometric and cardiometabolic resting data of the eutrophic, DM 1 and obese children are presented in table 1. Obese and DM 1 were younger than eutrophic children (*p*<0.001). Body mass of obese was higher than eutrophic (*p*<0.01). Obese also presented higher Z-score and waist circumference when compared with both eutrophic and DM 1 (*p*<0.001). Body fat was higher in DM 1 and obese compared with eutrophic (*p*<0.001) and, finally, diastolic blood pressure was higher in obese compared with both DM 1 and eutrophic (*p*<0.01). Glycated hemoglobin was measured to evaluate the glycemic control and, as expected, DM 1 presented higher values when compared with obese children (*p*<0.001).

Table 1 – Anthropometric and cardiometabolic parameter of eutrophic (n = 8), type 1 diabetic (DM 1; n = 8) and obese (n = 8) children.

Parameter	Eutrophic (n = 8)	DM 1 (n = 8)	Obese (n = 8)
Age (years)	11.7 ± 0.1	10.8 ± 0.2*	8.5 ± 0.6*
Body mass (kg)	38.3 ± 2	41.1 ± 2.1	58.4 ± 5.6*
Height (cm)	1.51 ± 0.02	1.49 ± 0.02	1.44 ± 0.05
Z-Score (BMI)	-0.55 ± 0.23	0.43 ± 0.27	3.92 ± 0.48*#
Body fat (%)	13.8 ± 1.0	20.7 ± 1.7*	31.1 ± 1.0*#
Waist circumference (cm)	63 ± 1	65 ± 1	83 ± 4*#
Systolic pressure (mmHg)	97 ± 7	104 ± 3	108 ± 5
Diastolic pressure (mmHg)	50 ± 3	66 ± 5	69 ± 4*
Heart rate (bpm)	76 ± 3	73 ± 4	83 ± 4
Glycated hemoglobin (%)	-	9.1 ± 0.8*	5.3 ± 0.4

Mean ± SD = standard deviation; DM 1 = Type 1 diabetes; *p<0.05 compared to eutrophic group; #p<0.05 compared to DM1 group;

Figure 1 – Physical activity level obtained by International Physical Activity Questionnaire (IPAQ) in eutrophic (n = 8), type 1 diabetic (DM 1; n = 8) and obese (n = 8) children. *p<0.05 compared to eutrophic group.

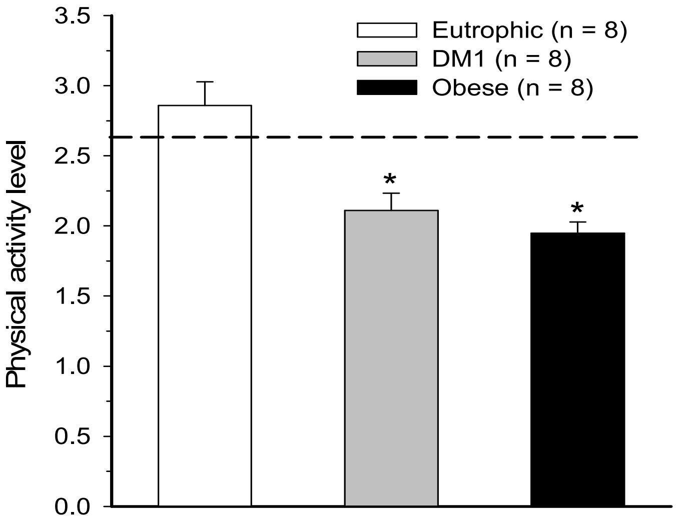
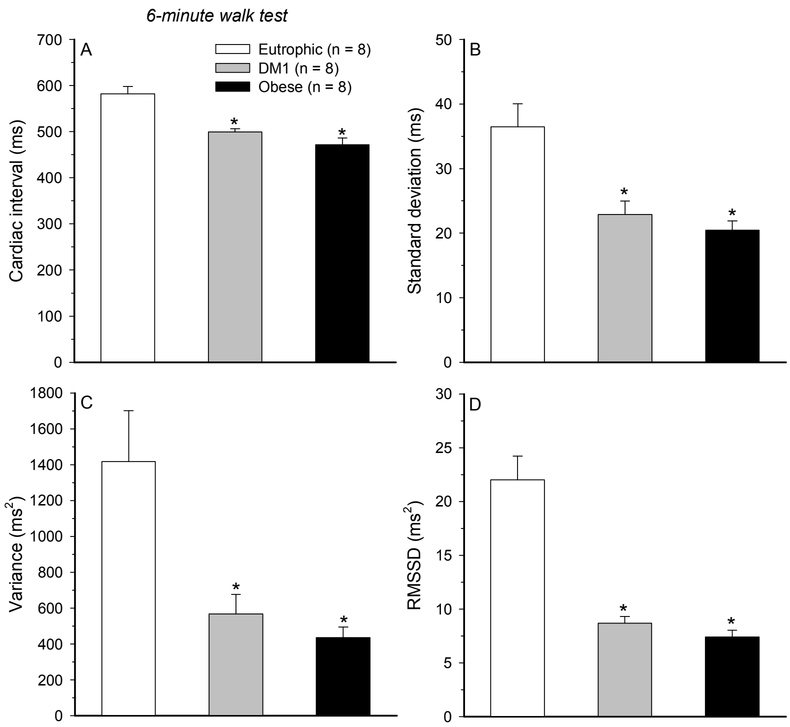


Figure 1 shown the physical activity level obtained by IPAQ. All children in Obese and DM 1 groups, and 4 children in eutrophic group (50%) presented physical activity level below that recommended from the questionnaire. Additionally, DM 1 and obese groups presented even lower levels when compared to the eutrophic group (p<0.001). Obese and DM 1 presented lower aerobic capacity, evaluated by shuttle run test, compared to eutrophic children (DM 1, 39.8 ± 0.6 mLO2·kg^{-1}·min^{-1}; Obese, 42.3 ± 1.1 mLO2·kg^{-1}·min^{-1}; eutrophic 45.2 ± 1.0 mLO2·kg^{-1}·min^{-1}, p<0.001).

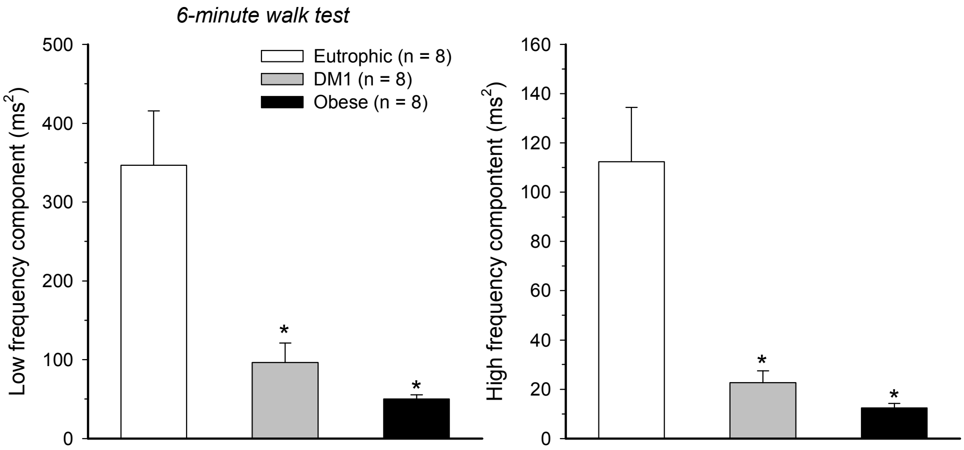
Figure 2 – Time-domain heart rate variability analysis in eutrophic (n = 8), type 1 diabetic (DM 1; n = 8) and obese (n = 8) children during the 6-minute walk test. RMSSD = Root mean square of the successive differences. *p<0.05 compared to eutrophic group.



Time-domain heart rate variability analysis in exercising eutrophic, obese and DM 1 children are presented in Figure 2. The mean cardiac interval (Fig. 2A), standard deviation (Fig. 2B), variance (Fig. 2C) and the RMSSD were reduced in DM 1 and obese when compared with de eutrophic children (p<0.001).

Figure 3 shown frequency-domain heart rate variability analysis in exercising eutrophic, DM 1 and obese children. Both low and high frequency components were reduced in DM1 and obese when compared with de eutrophic children ($p<0.001$).

Figure 3 – Frequency-domain heart rate variability analysis in eutrophic (n = 8), type 1 diabetic (DM 1; n = 8) and obese (n = 8) children during the 6-minute walk test. *$p<0.05$ compared to eutrophic group.



The associations between HRV parameters and physical activity level, obesity parameter (Z-score) and glycemic control (Hb1Ac) are presented in Table 2. Was found positive and significant moderate to very strong correlations between IPAQ and HRV parameters. Was also observed moderate to strong correlation between obesity evaluated by Z-score and HRV. Wasn't find correlations between glycemic control infer by Hb1Ac and HRV data.

Table 2 – Correlations between heart rate variability parameters and International Physical Activity Questionnaire (IPAQ) or Z-score or Glycated hemoglobin (Hb1Ac) of eutrophic (n = 8), type 1 diabetic (DM1; n = 8) and obese (n = 8) children.

	IPAQ (n = 24) *r*	*p-value*	Evan's criteria	Z-score (n = 24)	*p-value*	Evan's criteria	Hb1Ac (%; n = 16)	*p-value*	Evan's criteria
SD (ms)	0.59	<0.01	moderate	-0.56	<0.01	moderate	0.16	NS	very weak
Variance (ms^2)	0.69	<0.001	strong	-0.51	<0.02	moderate	0.14	NS	very weak
RMSSD (ms^2)	0.80	<0.001	very strong	-0.62	<0.01	strong	-0.10	NS	very weak
LF (ms^2)	0.68	<0.001	strong	-0.54	<0.01	moderate	0.10	NS	very weak
HF (ms^2)	0.65	<0.001	strong	-0.55	<0.01	moderate	0.04	NS	very weak

SD = Standard deviation; RMSSD = Root mean square of the successive differences; LF = low frequency component; HF = High frequency component.

Figure 4 – Correlation between Root mean square of the successive differences (RMSSD) of time-domain heart rate variability analysis and International Physical Activity Questionnaire (IPAQ) in eutrophic (n = 8), type 1 diabetic (DM 1; n = 8) and obese (n = 8) children during the 6-minute walk test.

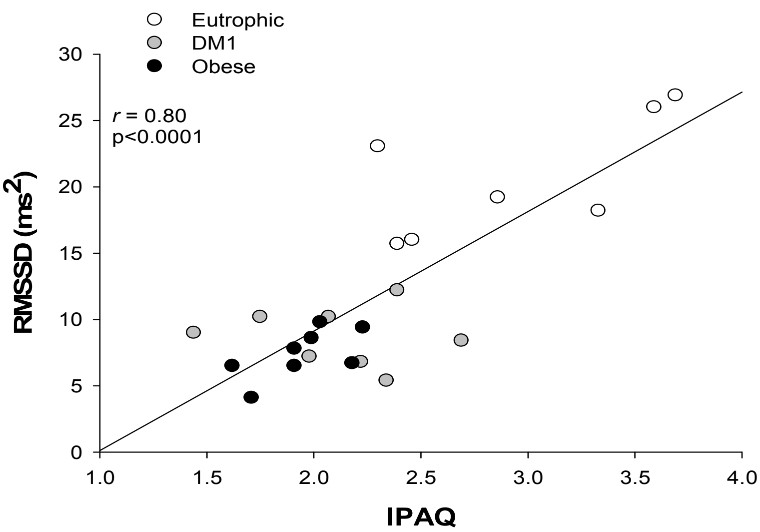


Figure 4 shown the association between IPAQ and cardiac vagal tonus evaluated by RMSSD. We found a very strong association between these parameters ($p<0.0001$).

Discussion

The main finding of the present study was that obese and DM1 children presented reductions in spectral parameters in the HRV in both time domain and frequency domain during physical exercise, indicating a reduced ANS ability to adapt acutely to exercise. Also, was showed that impairment in autonomic responses are directly associated with children's physical activity level and adiposity level in all groups was evaluated. Together, these data show that lower level of physical activity in childhood is associated with obesity and / or DM1 and may induce significant impairment to efferent ANS branches controlling cardiac function.

The association of physical activity levels with HRV is well demonstrated in the literature in obese (35, 20), DM 1 (7, 16) and eutrophic children (21, 28). However, in this study, we emphasize that even in obese children with DM 1, the level of physical activity was the variable that presented the highest correlation, even in comparison with the markers of obesity (Z Score and body fat %) and metabolic parameter (HbA1c). Despite this finding, the positive point is that the increase in physical activity levels and aerobic capacity, through exercise training and leisure activity, can improve HRV-related parameters (30, 37), reinforcing the regular practice of physical activity during childhood and adolescence.

In addition, studies have shown that individuals with lower fitness for performing daily exercises and activities have low cardiac autonomic responsiveness and blood pressure parameters in relation to individuals who exercise regularly (19, 39), in the same way, Palmeira et al. (6) identified an association between physical leisure activities and SDNN and RMSSD parameters in children. The results of the present study agree with those of Palmeira et al. (6). Together, the results of the studies indicate that RMSSD may be a more sensitive variable when assessing levels of physical activity and HRV. Additionally, the study by Chen et al. (7) found that children with DM 1 with low level of physical activity present reduced values of HRV during rest, but not during physical activity, which diverges from the results found in this study. A possible explanation for this difference is the intensity of the exercise performed. Fronchetti et al. (17) suggest that during exercise there is a threshold of HRV that occurs due to increased intensity and promotes reduction of vagal activity and increase of sympathetic activity. These changes influence the control of HR and limit HRV analysis.

The level of daily physical activity evidenced by the IPAQ results indicates that, on average, all groups did not perform the recommended minimum time of physical activity, 150 minutes per week at moderate or 75 vigorous intensities according to ACSM (2) and DSBD (12). It is noteworthy that only four children (50%) of the eutrophic group were classified as minimally active in the present study, presenting values for the IPAQ near and above 3. The low level of physical activity of the children with DM I or obese was reflected in the measured performance parameters, estimated VO2max and maximum speed. Corroborating with the results of our study, Green, Egana, Baldi et al. (19) indicated that sedentary individuals with DM have lower VO2max, cardiac output and lower arteriovenous difference in submaximal and maximal physical exercises. In the same way, Middelbeek, James-Todd, Patti et al. (29) and Pendergrass, Koval, Vogt et al. (32) demonstrated that sedentary individuals with DM or obesity have a reduction in the amount of glycolytic and oxidative pathway enzymes compared to those without the disease. This condition was also visualized by Komatsu, Barros Neto, Chacra et al. (24), however, exercise training was able to increase the exercise capacity of people with DM to values like those trained without DM. These data suggest that cardiovascular risk due to reduced oxidative capacity can be minimized by performing regular physical exercises, as well as promoting improvements in glycemic control.

In the present study, both DM 1 and obese children had a higher fat percent when compared to eutrophic children. In addition, Z-score was higher in obese compared to DM1 and eutrophic children. Moderate to strong correlations were found between the HRV spectral parameters and the Z-score, indicating that HRV reduction in response to exercise is associated with the high body fat values. The measurement of Z-score and fat percent are widely used as a function of the associations with cardiovascular diseases, including arterial hypertension (36; 27). The association between obesity and the reduction in frequency domain HRV parameters indicates that excess body fat induces impaired autonomic modulation in response to exercise. This may be related to obesity-induced cardiac neuropathy. Studies have shown that a lower baroreflex sensitivity is, partly, determined by efferent sympathetic and parasympathetic. The response of these efferent branches can be inferred through the analysis of the LF and HF components of the HRV. According to Goldstein et al. (18), low values of LF and HF components indicate poor baroreflex control. In the present study, DM 1 and obese children present strong attenuation of the modulation of both spectral components. It is important to note that arterial baroreflex is the main mechanism that buffer blood pressure oscillations. Decreases in baroreflex sensitivity are directly associated with higher blood pressure lability. Our data showed higher diastolic blood pressure in obese children when compared to DM1 or eutrophic children, corroborating the hypothesis of reduction of baroreflex regulatory capacity.

Body fat excess is considered a low-grade inflammation. In the intermediate obesity and in severe obesity, increased pro-inflammatory adipokines and macrophages infiltration in adipose tissue are observed. In overweight people, metabolic control becomes impaired; however, vascular function remains preserved. On the other hand, in severe obesity, autonomic cardiovascular function becomes inefficient (31). Systemic inflammation is associated with autonomic cardiac neuropathy. Alterations in the release of noradrenaline or acetylcholine in the sympathetic and parasympathetic nerve endings, respectively, as well as a down-regulation of the adrenergic or muscarinic receptors may explain HRV reductions found in the present study.

The study presents limitations regarding the small sample size, which limits the generalization of the data and, technically, the application of a more detailed statistical analysis, such as multiple regression. The assessment of the level of physical activity through a questionnaire, even with the validation of the same, could be better quantified by quantitative methods, such as pedometry, and the measurement of Hb1Ac in the eutrophic group could contribute to a better understanding of the influence of this marker on the values of HRV.

Conclusion

The results of the study indicate that the level of physical activity has a strong association with HRV, with lower levels in obese and DM 1 children. Associated with this, the low cardiorespiratory capacity identified, especially in obese and DM 1, reinforcing the importance of the practice of physical activity during childhood and adolescence as a protective factor for cardiometabolic outcomes.

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