

Prevalence of Risk Factors for Cardiovascular Disease in Adolescents with Type 1 Diabetes

Research Article

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Abstract

Aims: The objective of this study was to investigate the prevalence of hyperglycemia, dyslipidemia, overweight, hypertension and sedentary lifestyle as risk factors for cardiovascular diseases in adolescents with Type 1 Diabetes.

Methods: Adolescents (10-18 years) with type 1 diabetes participated in the study. Socioeconomic, demographic, biochemical data of glycemic control and lipid profile, blood pressure, anthropometric measurements and physical activity were collected. For the variables with normal distribution, the means and standard deviation were calculated. Chi-square test and Fisher's exact test ($p < 0.05$) were used for the categorical variables.

Results: 45 adolescents (55.6% female) with a mean age of 13.7 years ($SD \pm 2,292$) participated. Most participants had hyperglycemia (81% and 95% with fasting glycaemia and increased glycated hemoglobin, respectively). The high concentration of LDL cholesterol was present in 20% of the participants. 19% had arterial hypertension, with 6% of excess weight and 22% with cardiovascular risk assessed by waist circumference. Almost half of the adolescents did not practice any physical activity.

Conclusion: Adolescents with type 1 diabetes in the study had a high prevalence of risk factors for the development of cardiovascular diseases.

Keywords: Adolescents; Diabetes Mellitus, Type 1; Overweight; Dyslipidemias; Cardiovascular Diseases

Abbreviations: HbA1c: Glycated hemoglobin; HDL-C: High-Density Lipoprotein; LDL-C: Low-Density Lipoprotein; VLDL-C: Very Low-Density Lipoprotein; BMI: Body Mass Index

Introduction

Diabetes mellitus type 1 (DM1) is the result of the destruction of pancreatic beta cells with consequent insulin deficiency. Although this type of diabetes is less common, its increase is around 3% per year, especially among children. It is estimated that in the world there are more than half a million children up to 14 years of

age with DM1. Brazil occupies the third place in the ranking of the ten countries with the largest number of children, behind the United States of America and India [1]. Patients with diabetes have a higher risk of microvascular complications such as retinopathy, nephropathy and neuropathy, with consequent lower limb amputation, and also macrovascular diseases due to the constant state of hyperglycemia [2].

Morbimortality rates due to cardiovascular disease (CVD) show a two to four fold increase in patients with DM1 and in these, cardiovascular events account for up to 44% of total mortality [3]. As the appearance of these

complications usually occurs in adulthood, it is necessary to investigate the risk factors for these comorbidities as well as their early prevention [4]. Adult patients diagnosed with DM1 in childhood and without cardiovascular symptoms underwent exams and presented atherosclerotic processes, evidencing that it begins in childhood and accelerates in the presence of risk factors [3].

Under this perspective, the present study aimed to identify the prevalence of hyperglycemia, dyslipidemia, excessive weight, arterial hypertension and sedentary lifestyle as risk factors for cardiovascular diseases in adolescents with DM1.

Methods

Experimental Approach and Subjects

This was a cross-sectional study, which sampling was, by convenience, performed at the Endocrinology and Nutrition Service of a public reference hospital in the Center-West of Brazil. The sample size of 45 participants was based on a prevalence of 80% of inadequate glycemic control [5], with significance level of 5% and test power of 80%. The study participants were adolescents aged 10 to 18 years and 11 months [6] volunteers, of both sexes, with Type 1 Diabetes mellitus, regularly attended at the service.

Patients were invited to participate in the research during the waiting period for routine medical consultation. The excluded individuals were those diagnosed with other types of diabetes, celiac disease, growth hormone deficiency, chromosomal abnormalities and pregnancy. The study was approved by the Research Ethics Committee of the Federal University of Goiás under Protocol 127/11. Participants were previously consulted, along with their caregivers, about the interest in participating and after knowledge about the study signed the Informed Consent Form.

5.2. Socioeconomic and Demographic Data

Socioeconomic and demographic data were obtained through a direct interview with patients. The study variables were: sex, age, schooling of the adolescents and per capita income. Age was categorized in 10 to 15 and 16 to 18 years. The schooling was categorized in "1st stage of Elementary School", "2nd stage of Elementary School", "High school" and "Incomplete higher education". Per capita income was calculated based on the monthly income of the family distributed by the total number of people living with this income. Subsequently income was categorized into three levels of minimum wage (SM) that is determined by the Brazilian Constitution [7]. As for housing, basic sanitation conditions were assessed.

Glycemic Control and Lipid Levels

Biochemical data were obtained through routine laboratory tests presented at the consultation. For glycemic control, the levels of glycosylated hemoglobin (HbA1c) and fasting glycemia were evaluated. Analytical methods are recognized by the Brazilian Society of Diabetes, as well as cut-off points for adequacy and inadequacy of glycemic control [8]. As for the lipid profile, the serum levels of total cholesterol, low-density lipoprotein (LDL-cholesterol) very low-density lipoprotein (VLDL cholesterol), high-density lipoprotein (HDL-cholesterol) and triglycerides were evaluated, which cut-off points for "adequate" categorization were the values up to the maximum reference limit of the method.

Blood Pressure, Anthropometric Measures and Physical Activity Level

Blood pressure measurements were obtained using a digital oscillometric semiautomatic device, in three moments, with a minimum interval of two minutes between the measurements, following the instructions presented in the VI Brazilian Guidelines on Hypertension [9]. Values were classified according to age, sex and height.

The anthropometric measures were performed by the same researcher, as proposed by Gibson [10], in duplicate, non-consecutive, and the means were calculated. The weight was obtained with a portable platform, through digital and electronic scale, with a maximum capacity of 150 kilos and a sensitivity of 50 grams. The height was obtained using a stadiometer, with a variation of 1 mm and a maximum extension of 220 cm, attached to the wall without skirting.

The anthropometric classification of adolescents was performed according to the body mass index for age (BMI/Age) according to cutoff points, expressed in percentiles, proposed by the World Health Organization [6].

Measurements of waist circumference (WC) were performed with an inextensible flexible measuring tape, with a maximum length of 150 cm and a variation of 1 mm. The cut-off points proposed by Taylor, et al. [11] were used. The activities performed during twenty four hours were recorded with their respective physical activity coefficients, according to age and gender, and physical activity levels [12] were determined.

Statistical Analysis

The data were analyzed by the program Statistical Package of Social Sciences (SPSS) version 18.0. Descriptive statistics were used. Continuous variables were tested for normality by the Kolmogorov-Smirnov test. For the variables with normal distribution, the means and standard deviation were calculated. For the

categorical variables, the chi-square test and the Fisher's exact test were applied, $p < 0.05$.

Results

The sample consisted of 45 participants, predominantly female (55.6%) and mean age of 13.7 years old ($SD \pm 2.29$). Regarding the financial condition, 95.5% of the interviewees had monthly income per capita of up to two minimum wages (SM), characterizing it as a low-income population. The housing condition data presented that 51.1% of the

households had no sewage network and 17.8% had no treated water. The results showed no significant difference between genders (Table 1). The age group with the highest frequency of diagnosis of DM1 was between 0 and 10 years. Of the adolescents in the research, only 68.9% reported at home glycemic control (HGC). Of these, girls do it more often, two to three times a day. The predominant insulin therapy was with neutral protamine Hagedorn insulin (NPH) and Regular insulin (Table 2).

Variables	Adolescents					p*
	Total	Boys		Girls		
		n	(%)	n	(%)	
Age (years)						
10 + 15	34	16	35.6	18	40.0	0.73 ²
16 + 19	11	4	8.9	7	15.6	
Scholarity (adolescents)						
Elementary school-1 st phase	12	6	13.3	6	13.3	0.55 ¹
Elementary school-2 nd phase	22	11	24.4	11	24.4	
High school	10	3	6.7	7	15.6	
University education (incomplete)	1	0	0	1	2.2	
Per capita income						
< 1MW ³	41	18	40	23	51.1	0.97 ¹
1 + 2 MW ³	2	1	2.2	1	2.2	
2 - + 5 MW ³	2	1	2.2	1	2.2	
Social assistance						
Yes	12	7	15.6	5	11.1	0.25 ¹
No	33	13	28.9	20	44.4	
Potable water						
Yes	37	16	35.6	21	46.7	1.00 ²
No	8	4	8.9	4	8.9	
Sewage system						
Yes	22	11	24.4	11	24.4	0.46 ¹
No	23	9	20.0	14	31.1	

*Statistical significance ($p < 0.05$); ¹Chi-square test; ²Fisher exact test; ³MW: National minimum wage (US\$ 275).

Table 1: Sociodemographic and economic characteristics of the participants.

Variables	Adolescents					p*
	TOTAL	Boys		Girls		
		n	(%)	n	(%)	
Age at diagnosis (years)						
0 + 10	34	15	33.3	19	42.4	1.00 ₂
11 + 19	11	5	11.1	6	13.3	
Time w/diagnosis (years)						
0 + 10	38	18	40.0	20	44.4	0.43 ₂
11 + 19	7	2	4.4	5	11.1	
Monitoring glycaemia						
Yes	31	14	31.1	17	37.8	0.88 ₁
No	14	6	13.3	8	17.8	
Number of monitoring glycaemia/day						
≤1	8	4	8.9	4	8.9	0.04 ₁
2 + 3	15	3	6.7	12	26.7	
4 + 6	7	6	13.3	1	2.2	

≥7	1	1	2.2	0	0	
Insulin injection áreas						0.21 ¹
Arms	8	5	11.1	3	6.7	
Abdômen	5	1	2.2	4	8.9	
Buttocks	1	0	0	1	2.2	
Thighs	3	0	0	3	6.7	
Rotation of location	28	14	31.1	14	31.1	
Insulin						0.48 ¹
NPH + Regular	30	13	28.9	17	37.8	
Analogs (long and rapid-acting)	7	2	4.4	5	11.1	
NPH + rapid-acting	7	4	8.9	3	6.7	
Long-acting + Regular	1	1	2.2	0	0	

*Statistical significance (p<0.05); ¹Chi-square test; ²Fisher exact test; NPH: Neutral protamine Hagedorn

Table 2: Therapy characteristics of adolescents with type 1 diabetes.

The adolescents of the study had an 81% inadequacy of glycemic control demonstrated by fasting glycaemia and only 5% of the adolescents presented HbA1c values up to the upper limit of recommendation. The frequency of dyslipidemia was also elevated, mainly by the serum

levels of total cholesterol and LDL-cholesterol. Other risk factors, such as hypertension (18.5%), sedentary lifestyle (48.9%), overweight (6.1%) and inadequate waist circumference (21.9%) also had an increased prevalence (Table 3).

Variables	n	(%)
Fasting glucose (n=42)		
Adequate	8	19.0
Inadequate	34	81.0
HbA1c (n=37)		
Adequate	2	5.4
Inadequate	37	94.6
Serum Cholesterol (n=45)		
Adequate	37	82.2
Inadequate	8	17.8
HDL-C (n=45)		
Adequate	39	86.7
Inadequate	6	13.3
LDL-C (n=45)		
Adequate	36	80.0
Inadequate	9	20.0
VLDL-C (n=45)		
Adequate	42	93.3
Inadequate	3	6.7
Tryiglycerides (n=45)		
Adequate	41	91.1
Inadequate	4	8.9
Blood pressure (n=27)		
Adequate	21	77.8
Inadequate	5	18.5
Physical activity level (n=45)		
Sedentary	22	48.9
Low physical activity	15	33.3
Moderate physical activity	8	17.8
High physical activity	0	0
BMI/age (n=33)		
Underweight	6	18.2
Normal	25	75.8
Overweight	2	6.1

Waist Circumference (n=32)		
Adequate	25	78.1
Augmented	7	21.9

HbA1c: glycated hemoglobin, HDL-C: high-density lipoprotein; LDL-C: low-density lipoprotein; VLDL-C: very low-density lipoprotein; BMI: Body mass index

Table 3: Risk factors for cardiovascular diseases in adolescents with type 1 diabetes.

Discussion

Socioeconomic and demographic profile of the population studied, such as the average age, the prevalence of women and the prevalence of family income with less than two minimum wages, are explained mainly because the patients were part of the Brazilian public health system. These data are similar to those reported in other studies in Brazil [13-15].

The increase in the incidence of DM1 and the higher prevalence of participants diagnosed before 10 years of age has been observed in epidemiological studies. Patterson, et al. [16] observed a higher incidence between the ages of 5-9 years old and an estimate of a greater annual increase in new cases between the ages from 0 to 4 years old, confirming that, in relative terms, the incidence of DM1 will be higher at increasingly younger ages. Derraik, et al. [17], although observing an increase in mean age at diagnosis from 7.6 to 8.9 years and an increase in the incidence among children aged 10 to 14 years old (27.5/100.000 inhabitants), compared to those aged 5 to 9 years old (25.4/100.00 inhabitants) and from 0 to 4 years old (14.9/100.000 inhabitants) showed a constant increase in new cases in children under 15 years old. These findings may explain the higher prevalence of adolescents in the study with diagnosis before 10 years old.

Glycemic monitoring should be performed at least six times a day to identify blood glucose and adjust insulin in intensive therapy. This recommendation is well above that observed in this study. Most children and adolescents, in order to reduce fingertip examination and save reagent tapes at high cost, only carry out preprandial measurements. This practice is associated with poor glycemic control resulting in higher episodes of hypo and hyperglycemia, as well as higher values of HbA1c [18,19].

Regarding the insulin regimen, insulin analogues have demonstrated efficacy in relation to human insulin because of the greater flexibility of the therapy, a decrease in episodes of severe hypoglycemia and a significant reduction in HbA1c [13,20]. The Brazilian public health system, up until 2016, provided only NPH and Regular insulin for the treatment of diabetes because of the cost and the absence of conclusive studies on the advantages of insulin analogues.

Currently, through price negotiation and specific protocol follow-up, these insulins can be incorporated into the treatment with system coverage [21]. However, this reality has not yet contemplated the adolescents of the study whose majority still only receives insulins from the public health system. This may be contributing to the participants' poorer glycemic control. It is observed, therefore, that treatment and adherence characteristics may influence the worse glycemic control.

According to the Brazilian Society of Diabetes [8], the use of HbA1c is recommended for evaluation of glycemic control in clinical practice. Although fasting glycaemia (FG) alone is still widely used, it is insufficient to follow the glycemic control of patients, as it reflects only a timely measure, whereas HbA1c reflects the history of glycaemia over 120 days prior to collection. HbA1c targets for children and adolescents vary from less than 6% by the International Society for Pediatric and Adolescent Diabetes to less than 7.5% by the American Diabetes Association. The glycemic goal, especially in adolescence should be individualized, considering the family commitment and patient adherence.

The deterioration in glycemic control observed by HbA1c was associated with age at diagnosis by Clements, et al. [22]. The authors observed that adolescents diagnosed at 10 years of age presented worse glycemic control in the first five years, compared to patients diagnosed at a younger age. In the present study, although most adolescents were diagnosed before 10 years of age, almost all presented HbA1c above the recommendation.

According to Flora and Gameiro [23], older adolescents carry a greater responsibility for self-care inherent in controlling the disease, but they have a weak relationship with health centers, which are still the parents' responsibility. This transition process, in which there is a search for autonomy and independence from parents and decision making on their own, may reflect in inadequate care for DM1 [24]. Food intake may also influence glycemic control in adolescents [25]. Carbohydrate counting is a nutritional therapy that has shown favorable results in relation to HbA1c levels [26].

It is estimated that adults with controlled diabetes have a similar lipid profile to individuals without the disease, and it has been shown that better glycemic

control may decrease or normalize the lipid profile. However, in the presence of hyperglycemia, dyslipidemia becomes an important risk factor for cardiovascular diseases in patients with DM1 [27]. The results of a study with Indian adolescents with DM1 showed a positive correlation between HbA1c \geq 8% and serum levels of total cholesterol and LDL-cholesterol [28]. Inadequate glycemic control is also associated with an increased need for insulin and accumulation of abdominal fat [29]. The use of high doses of insulin, in turn, is also associated with weight gain [30].

According to GUY et al. [31], however it is possible to identify changes in the lipid profile of young people with DM1, even in those newly diagnosed with adequate glycemic control, these changes are higher in patients with inadequate glycemic control. This correlation between inadequate metabolic control and fractions of total and elevated LDL cholesterol was found in a comparison study among diabetic and non-diabetic children and adolescents [32].

Another important cardiovascular risk factor, hypertension, which prevalence was high among the adolescents of the present study, may already begin in the pediatric age group and is more common in patients with DM1. In the study by Santos, et al. [33], in which the diastolic function was evaluated in children and adolescents with DM1, diastolic changes were evidenced in those with normal ejection fraction. These changes contribute to increase peripheral vascular resistance and the appearance of hypertension. Although not investigated in the present study, inflammation should be considered as it is a central process for the development of atherosclerosis and particularly affects patients with DM1. Its mechanism of action in these patients involves factors such as hyperglycemia, excess adiposity or alteration in the distribution of body fat [34].

Díaz-Cárdenas, et al. [35] observed a lower prevalence of arterial hypertension than that observed in the present study. However, they described an inadequate metabolic control in almost 80% of the patients, especially those older than 13 years, overweight or obese in 26.6% of the patients. In relation to the excess weight and distribution of body fat, in studies carried out by Alvarado, et al. [36] and Junior, et al. [37], both in adolescents with DM1, the prevalence was also similar to that of the present study. These results cannot be ignored. Some studies have demonstrated a trend of greater weight gain compared to height in children with DM1 when they enter the puberty stage [29,30,38].

Excess weight and abdominal fat are considered independent risk factors for cardiovascular disease in people without diabetes, but are also related to each other. In the presence of DM1 the studies have still been

trying to establish its impact. The patient with DM1 was traditionally characterized as thin, but the prevalence of overweight has increased in these patients [34]. In a medical cohort study, it was evidenced that the average waist circumference of diabetics was higher when compared to healthy individuals [39].

Ferranti et al. emphasize that cardiovascular risks are more common in young people with DM1, that these patients are subjected to the epidemic of obesity and its association with the metabolic syndrome, and that studies have been devoted to uncovering when weight or glycemic control are more important in determining cardiovascular risk factors. Lifestyle changes involving healthy eating with low amounts of saturated fat and salt, increased consumption of fruits and vegetables, and regular physical activity are recommendations in guides such as the American Diabetes Association (ADA), American Academy of Pediatrics (AAP) and the American Heart Association (AHA) for the prevention and control of risk factors [34].

Physical activity, together with glycemic control and insulin-feeding regimen, is one of the cornerstones in the treatment of DM1, besides promoting beneficial effects on patient's quality of life, body composition, lipid profile, insulin sensitivity and in long-term glycemic control demonstrated by lower HbA1c values [40]. Adolescents generally practice less time of physical activity than recommended. Schools have decreased, or even withdrawn, the period of physical activity to increase the time of dedication to studies. The sedentarism is further aggravated by leisure activities that are mainly electronic games and television. The same happens with young people with DM1 [41].

In addition to sedentarism being a trend among youngsters, parents of adolescents with DM1 are concerned about the impact of physical activity on the development of hypoglycemia and they ultimately discourage their children from exercising. As meta-analysis studies have shown that increased levels of physical activity do not increase episodes of severe hypoglycemia, parents should be given guidance to monitor blood glucose levels before, during and after physical activity. Inadequate glycemic control contributes to episodes of hypoglycemia during physical activity [42,43]. Many young people with DM1 still rely on parental help for care in hypoglycemia. If parents are well-oriented, act as an example, support and instill autonomy in their children, they will be encouraged to do exercise, especially those with higher intensity [41].

Conclusion

The present study demonstrated that the population studied, due to its glycemic control profile, prevalence of dyslipidemia and arterial hypertension, presence of

excess weight, high abdominal fat frequency and sedentary lifestyle are at cardiovascular risk. The study has limitations because it was carried out in a single service center, with a limited number of participants, not allowing full representation of the adolescents with DM1 and also not allowing inference and statistical hypotheses to be tested. However, these results support the urgent need for a better screening of these risk factors, the adoption of control measures, and the introduction of diabetes education with emphasis on home glycemic control, adequate and balanced dietary intake and physical activity practice.

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