Revista Eletrônica
Acervo Saúde
Electronic Journal Collection Health ISSN 2178-2091

Cardiovascular risk factors associated with hypothyroidism in children and adolescents with Down Syndrome

Fatores de risco cardiovascular associados ao hipotireoidismo em crianças e adolescentes com Síndrome de Down

Factores de riesgo cardiovascular asociados al hipotiroidismo en niños y adolescentes con Síndrome de Down

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ABSTRACT

Objective: To evaluate the association between cardiometabolic risk factors and treated hypothyroidism in children and adolescents with Down Syndrome. **Methods:** Of 51 patients with Down Syndrome, 20 met the eligibility criteria and participated in a cross-sectional study, underwent clinical examination, laboratory tests aimed at evaluating thyroid function, insulin resistance and lipids. **Results:** Age ranged from 4.0 to 19 years (mean:11.6), 14 were pubertal, 8(40%) had acanthosis nigricans, 7(35%) were overweight/obese and 3(15%) had increased abdominal circumference, Z-BMI was higher in males (p=0.034). Elevations of insulin were observed in 7(35%) patients of the HOMA-IR index in 5(25%), of triglycerides in 12(60%), ferritin in 6(30%), reduction of HDL-cholesterol in 10(50%). Triglycerides and non-HDL-cholesterol were significantly higher in males. Free T4 concentrations were higher in females (p=0.043). The variables Z-BMI and waist circumference showed an inverse correlation with Free T4 and Total T3 and a direct correlation with insulin, ferritin and triglycerides concentrations. **Conclusion:** The data from the present study indicate the need to optimize the treatment of hypothyroidism, prevention and reduction of cardiometabolic risk factors, especially in males.

Keywords: Hypothyroidism, Down syndrome, Risk factors, Child, Adolescent.

RESUMO

Objetivo: Avaliar a associação entre fatores de risco cardiometabólicos e hipotireoidismo tratado em crianças e adolescentes com Síndrome de Down. **Métodos:** Dos 51 pacientes com Síndrome de Down, 20 preencheram os critérios de elegibilidade e participaram de um estudo transversal, foram submetidos a exame clínico, exames laboratoriais visando avaliar função tireoidiana, resistência insulínica e lipídios. **Resultados:** A idade variou de 4,0 a 19 anos (média: 11,6), 14 eram púberes, 8 (40%) tinham acantose nigricans, 7 (35%) estavam com sobrepeso/obesidade e 3 (15%) tinham circunferência abdominal aumentada, Z- O IMC foi maior no sexo masculino (p=0,034). Foram observadas elevações da insulina em 7(35%) pacientes, do índice HOMA-IR em 5(25%), dos triglicerídeos em 12(60%), da ferritina em 6(30%), redução do HDL-colesterol em 10 (50%). Os triglicerídeos e o colesterol não HDL foram significativamente maiores nos homens. As concentrações de T4 livre foram maiores no sexo feminino (p=0,043). As variáveis Z-IMC e circunferência da cintura apresentaram correlação inversa com T4 Livre e T3 Total e correlação direta com concentrações de insulina, ferritina e triglicerídeos. **Conclusão:** Os dados do presente estudo indicam a necessidade de otimização do tratamento do hipotireoidismo, prevenção e redução dos fatores de risco cardiometabólicos, principalmente no sexo masculino.

Palavras-chave: Hipotireoidismo, Síndrome de down, Fatores de risco, Criança, Adolescente.

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SUBMETIDO EM: 10/2024 | **ACEITO EM: 10/2024** | **PUBLICADO EM: 12/2024**

RESUMEN

Objetivo: Evaluar la asociación entre factores de riesgo cardiometabólico y hipotiroidismo tratado en niños y adolescentes con Síndrome de Down. **Métodos:** De 51 pacientes con Síndrome de Down, 20 cumplieron con los criterios de elegibilidad y participaron en un estudio transversal, se les realizó examen clínico, exámenes de laboratorio destinados a evaluar la función tiroidea, la resistencia a la insulina y los lípidos. **Resultados:** La edad osciló entre 4,0 y 19 años (media: 11,6), 14 eran púberes, 8 (40%) tenían acantosis nigricans, 7 (35%) tenían sobrepeso/obesidad y 3 (15%) tenían circunferencia abdominal aumentada, Z- El IMC fue mayor en los hombres (p=0,034). Se observaron elevaciones de la insulina en 7 (35%) pacientes, del índice HOMA-IR en 5 (25%), de los triglicéridos en 12 (60%), de la ferritina en 6 (30%), reducción del colesterol HDL en 10 (50%). Los triglicéridos y el colesterol no HDL fueron significativamente más altos en los hombres. Las concentraciones de T4 libre fueron mayores en el sexo femenino (p=0,043). Las variables Z-IMC y circunferencia de cintura mostraron correlación inversa con T4 libre y T3 total y correlación directa con las concentraciones de insulina, ferritina y triglicéridos. **Conclusion:** Los datos del presente estudio indican la necesidad de optimizar el tratamiento del hipotiroidismo, la prevención y reducción de los factores de riesgo cardiometabólico, especialmente en el sexo masculino.

Palabras clave: Hipotiroidismo, Síndrome de down, Factores de riesgo, Niño, Adolescente.

INTRODUCTION

Trisomy 21 mainly caused the presence of a supernumerary chromosome 21, is the most frequent autosomal aneuploidy. The Down Syndrome (DS) phenotype involves manifestations that affect multiple bodily systems and individuals with DS can present hypothyroidism and commonly congenital heart defects (CHDs) (ANTONARAKIS SE, et al., 2020). It is the most common chromosomal disorder, with a prevalence of 1:700 to 1:1500 live births, justifying its study in various clinical, laboratory and molecular aspects (AMR NH, 2018).

The main endocrine disease associated with DS is hypothyroidism, with prevalence rates ranging form 3 to 54% and with an increasing prevalence with age (WHOOTEN R, et al., 2018; ANTONARAKIS SE, et al., 2020). The presentation and etiology of hypothyroidism in DS suggests a spectrum, ranging from congenital hypothyroidism to overt hypothyroidism or even subclinical (SH) characterized by serum TSH above the upper limit of the reference range, with normal thyroid hormone concentrations (AMR NH, 2018).

The most common etiology for acquired hypothyroidism is chronic autoimmune thyroiditis (or Hashimoto's thyroiditis) characterized by the presence of anti-thyroperoxidase and anti-thyroglobulin autoantibodies. Many cases of overt or even subclinical hypothyroidism do not have autoimmune markers, raising doubts about the etiology, which has motivated additional investigations (FARIA CD, et al.. 2011; IUGHETTI L, et al., 2014; AVERSA T, et al., 2015).

Around 40-50% of people with DS have CHDs such as atrioventricular septal defects (~45%), ventricular septal defects (~35%), atrial septal defects (~8%), persistent ductus arteriosus (~7%) and tetralogy of Fallot (~4%). With advances in cardiac surgery and clinical treatments, these occurrences are detected and corrected early, however other cardiac complications can lead to major cardiovascular events capable of threatening life (SOBEY CG, et al., 2015; SANTORO M, et al., 2018; CILHOROZ BT, et al., 2022).

It is worrying in DS the increased prevalence of overweight/obesity associated to cardiometabolic risk factors, which can add to cardiac abnormalities and contribute to an unfavorable outcome (BERTAPELLI F, et al., 2016; WHOOTEN R, et al., 2018; ANTONARAKIS SE, et al., 2020). Actually, overweight/obesity is a serious public health problem, generating great socioeconomic impact and patients with DS are inserted in the same context of energy imbalance (NCD RISK FACTOR COLLABORATION, 2024). Furthermore, it can be associated with untreated or even subclinical hypothyroidism, interfering in growth (BERTAPELLI F, et al., 2016).

The association of these conditions results in a greater chance of metabolic abnormalities, thromboembolic phenomena and cerebrovascular accident (CVA), which are more prevalent in this population, even at an age younger than 50 years (SOBEY CG, et al., 2015). Based on these considerations, the main objective of the present study was to evaluate cardiometabolic risk factors in children and adolescents with DS and treated hypothyroidism, therefore compensated, on an outpatient basis at the Pediatric Endocrinology Unit of the Endocrinology and Metabolism Discipline of the Federal University of Triângulo Mineiro (UFTM) in Uberaba/MG.

METHODS

This is a cross-sectional study aimed at patients with DS diagnosed with hypothyroidism and who receive treatment and undergo regular follow-up. It was approved by the Ethics Committee of the Federal University of Triângulo Mineiro/UFTM (CAAE: 69329017.0.0000.5154, opinion number: 5.487.807). Of a total of 51 selected patients, 20 met the research eligibility criteria. Ages ranged between 4 and 19 years at the time of assessment. The inclusion criteria were: diagnosis of DS confirmed by karyotype examination, associated to treated hypothyroidism whether congenital, subclinical or overt, undergoing regular follow-up and signature of the terms of responsibility by the parents/guardians and adolescents.

The exclusion criteria were systemic diseases capable of interfering with the data obtained, the failure to locate patients for the research procedures, the non-acceptance in participate and the irregular attendance at the outpatient clinic during the period in which the study was conducted, namely between January and December 2023. All patients underwent detailed anamnesis and physical examination. Weight was obtained on a digital electronic scale with capacity of up 150 kg and 100g precision (Filizola, São Paulo, Brazil). Height was measured in upright position, on a wall stadiometer, model E150A (Tonelli, Crisciúma, Brazil).

Body mass index (BMI) was calculated dividing weight (kg) by squared height (m^2) (kg/m^2). Body mass index (Z-BMI) score was used do define nutricional status in DS individuals according to BERTAPELLI F, et al., 2016. Individuals were considered as overweight (+1≤ Z-BMI < 2) and obese (Z-BMI ≥ 2) (BERTAPELLI F, et al., 2017).

Physical examination included search of clinical signs of insulin resistence, as *acanthosis nigricans* in the nech, axila, elbow, and inguinal region. The abdominal circumference (AC) was measured with the individual in upright position at the midpoint between the lower margin of the last rib and the border of the iliac crest, after a normal expiration, with inextensible metric tape in millimeters (PALHARES HMDC, et al., 2018; NOGUEIRA-DE-ALMEIDA CA, et al., 2020).

Three measurements of blood pressure (BP) were taken with a minimum interval of two minutes and a mean values were calculated: blood pressure ≥ 95 percentile (P95) for age, gender and height were considered high (SOCIEDADE BRASILEIRA DE PEDIATRIA, 2019). For patients diagnosed with congenital hypothyroidism, clinical and/or laboratory data available in the medical records were used, and in many cases, parents provided us with the heel prick test report.

Confirmatory data for primary hypothyroidism were obtained from the medical records and everyone who presented TSH ≥ 10mIU/mL at one or two moments was being treated with doses of L-thyroxine ranging from 25 to 50µg per day (PALHARES HM, et al., 2012). In order to reassess the control and general etiology of hypothyroidism TSH, Free T4, Total T3, anti-TPO, anti-TG antibodies seric concentrations, thyroid ultrassonography was obtained as well as biochemical data considered cardiometabolic laboratory markers (PALHARES HMDC, et al., 2018; NOGUEIRA-DE-ALMEIDA CA, et al., 2020).

The laboratory tests were conducted, after 10 to 12 hours of fasting, and blood sample was collected by peripheral venous puncture for the following tests: fasting glycemia, glycated hemoglobin (HbA1c), basal insulin, total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, and ferritin. Serum concentrations of total cholesterol (T-Chol), HDL-cholesterol (HDL-Chol), tryglicerides (T), were measured by the enzimatic colorimetric method, glycemia by the enzymatic method with hexokinase. Samples was processed in COBAS 6000 module C501 (Roche Diagnóstica, São Paulo, Brazil).

Serum LDL cholesterol (LDL-Chol) concentrations were calculated on the Friedwald equation. HbA1c determined by Immunoturbidimetric method and Ferritin by Electrochemiluminescence. In addition, these data were analysed according to the Brazilian Association of Nutrology for the diagnosis and treatment of metabolic syndrome in children and adolescents (NOGUEIRA-DE-ALMEIDA CA, et al., 2020). HOMA-IR index (homeostasis model assessment insulin resistance index) was used to evaluate insulin resistance after being obtained by the calculation of the product of insulin (microU/mL) and fasting glycemia (mmol/L) divided by 22.5. The cutoff used was higher or equal to 2.5 for prepubertals and greater or equal to 3.43 for pubertals of both genders (GARCÌA CUARTERO B, et al., 2007; MADEIRA IR, et al., 2008).

TSH, Free T4, Total T3, fasting insulin and ferritin was determined by elctrochemiluminescence method and processed in the COBAS 6000 module C601. Anti-TPO, anti-TG was determined by Chemiluminescence and Electrochemiluminescence, respectively. The ultrasound scans were performed at the Unit of Radiology and Imaging of Hospital das Clínicas-UFTM with a HD II US apparatus (Philips Medical Systems; Bothell, WA, USA) and the scan data were analysed according to Zimmermann MB, et al., (2004).

Collected data was plotted in an Excel spreadsheet and later analyzed in SPSS (Statistical Package for Social Sciences) version 20. Data were submitted to descriptive analysis. The Kolmogorov-Smirnov test was used to verify normatilies of variables, and the homogeneity of variances was checked by the Levene test. Comparisons of data of interest employed. Student-t test when data had normal variance distribution and Mann-Whitney test when these conditions were not met. Correlation coefficients investigated association between variables. The level of significance for all inferencial procedures was at 5%.

RESULTS

Patients presented mean age of 11.6 years, months ranging from 4 to 19 years, 10 female and 10 male patients, with no statistical difference between them in age or in pubertal development (**Table 1**). This table also represented clinical variables related to cardiometabolic risks. There was no difference between the sexes except for the significantly higher Z-BMI in males (p= 0.034).

Table 1 - Clinical data of children and adolescents with Down Syndrome assisted at the Pediatric Endocrinology outpatient clinic at UFTM, Uberaba-MG.

Parameters analyzed	Female - (n = 10)	Male - (n = 10)	Total - (n = 20)
Age (years)	11.8 (4.0 - 18.0)†	11.4 (4.0 - 19.0)	11.6 (4.0 - 19.0)
Prepubertal / Pubertal	3 / 7	3 / 7	6 / 14
AN (present / absent)	3 / 7	5 / 5	8 / 12
BMI (Kg/m^2)	23.6 (14.0 - 33.0)	27.2 (16.7 - 38.5)	25.4 (14.0 - 38.5)
Z-BMI	0.29 (-1.3 - 1.5)	1.3 (0.04 - 2.7)*	0.79 (-1.3 - 2.7)
AC (cm)	74.9 (51.0 - 89.0)	84 (60.0 - 104.0)	79.5 (51.0 - 104.0)
SBP (mmHg)	101.0 (90.0 - 118.0)	107.2 (90.0 - 123.0)	103.9 (90.0 - 123.0)
DBP (mmHg)	63.0 (50.0 - 80.0)	68.3 (60.0 - 95.0)	65.8 (50.0 - 95.0)

Note: †: Data expressed as average (min-max); *: Z-BMI male > female, p: 0.034 (Student t-test); AN: acanthosis nigricans; AC: abdominal circumference; BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure.
Source: Azzuz JPRG, et al., 2024.

After analyzing medical records, it was found 15 patients with overt primary hypothyroidism, 5 of them (2 men and 3 women) with positive anti-thyroid antibodies and, therefore due to chronic autoimmune thyroiditis (CAT). Three patients presented with subclinical hypothyroidism (SH), were monitored for a period and were medicated when TSH reached concentrations above 10μIU/mL, and two patients had congenital hypothyroidism (CH). All patients were receiving L-thyroxine, (25 and 150μg/day) and had normal Free T4 and Total T3 and thyroid volumes were at the lower limit or low. When comparing thyroid variables between the genders, it was observed that Free T4 concentrations were significantly higher in females (p=0.043). The other data showed no differences and were represented in (**Table 2**).

The laboratory variables related to cardiometabolic risk were represented in **Table 3**. No differences were observed between the genders, except in relation to higher n-HDL-cholesterol in males (p=0.05) and borderline in relation to triglycerides also higher in males. In percentage terms, 35% of cases showed elevations in basal insulin, HOMA-IR (25%), triglycerides (60%) and ferritin (30%), and these percentages, except for triglycerides, were higher in males. HDL-cholesterol concentrations were equally decreased in both genders (**Table 4**).

A spectrum of the nutritional status from underweight (15%), overweight (25%), risk of obesity (5%) and obesity (10%) was observed. Overweight/obesity was present in 50% of men, with the other variables AC, AN, SAH also being more frequent in males (**Table 4**).

Table 2 - Laboratory and ultrasound data of the thyroid of children and adolescents with Down Syndrome attended at the Pediatric Endocrinology outpatient clinic at UFTM, Uberaba-MG.

	Female - (n = 10)	Male - (n = 10)	Total - (n = 20)
TSH (µUI/mL)	2.96 (0.33 - 5.95)	3.03 (0.79 - 5.80)	3.0 (0.33 - 5.95)
Free T4 (ng/dL)	1.21 ± 0.17 (0.90 - 1.49)*	1.02 ± 0.21 (0.70 - 1.36)	1.11 ± 0.21 (0.68 - 1.49)
Total T3 (ng/mL)	1.53 ± 0.60 (0.87 - 3.13)	1.34 ± 0.32 (0.88 - 1.92)	1.44 ± 0.50 (0.87 - 3.13)
Anti-TPO (UI/mL)	19.95 (0.01 - 121.80)	1.75 (0.22 - 5.60)	10.40 (0.01 - 121.80)
Anti-TG (UI/mL)	18.97 (2.21 - 147.60)	9.63 (1.16 - 59.54)	14.30 (1.16 - 147.60)
Thyroid – US(cm^3)	2.15 (0.60 - 4.20)	2.77 (1.49 - 3.50)	2.42 (0.60 - 4.20)

Note: * Female > Male, p: 0.043 (Student t-test); Reference value: TSH: 0.35 - 4.9; Free T4: 0.70 - 1.48; Total T3: 0.60 - 1.81; Anti-TPO (anti-thyroperoxidase antibody): < 5.61; Anti-TG (anti-thyroglobulin antibody): < 4.11; TSH: hormônio tireoestimulante; US: thyroid volume
Source: Azzuz JPRG, et al., 2024.

Table 3 - Laboratory data associated with cardiometabolic risk in children and adolescents treated at the Pediatric Endocrinology outpatient clinic at UFTM, Uberaba-MG.

	Female - (n = 10)	Male - (n = 10)	Total - (n = 20)
Fasting blood glucose (mg/dL)	87.7 (78 - 115)	85.6 (73 - 93.5)	86.62 (73 - 115)
HbA1c (%)	4.96 ± 0.35 (4.4 - 5.60)	5.17 ± 0.2 (4.8 - 5.4)	5.06 ± 0.29 (4.4 - 5.6)
Basal insulin (µUI/mL)	9.37 (2.7 - 15)	13.51 (1.7 - 30.5)	11.44 (1.7 - 30.5)
HOMA-IR Index	2.09 (0.57 - 3.97)	2.91 (0.31 - 6.99)	2.5 (0.31 - 6.99)
Ferritin (ng/mL)	131.6 (54.7 - 498)	137 (60.87 - 308.2)	134.3 (54.7 - 498)
Total cholesterol (mg/dL)	162.2 (149 - 184)	167 (154 - 188)	164.6 (149 - 188)
HDL-Chol (mg/dL)	45.09 (36 - 59)	41.57 (27 - 54)	43.33 (27 - 59)
LDL-Chol (mg/dL)	99.5 (80 - 119)	102 (82 - 123)	100.8 (80 - 123)
n-HDL-Chol (mg/dL)	111 (55 - 141)	125.4 (108.4 - 146)*	118.2 (55 - 146)
Triglycerides (mg/dL)	85.14 (53 - 147)	118 (59.4 - 207)**	101.6 (53 - 207)

Note: *: Male > Female, p: 0.05 (Mann-Whitney Test); **: Male > Female, p: 0.06 Borderline; VR: Fasting blood glucose; HbA1c: glycated hemoglobin; HOMA-IR: Homeostatic Model Assessment - Insulin Resistance; Students' t Test: values expressed in mean ± standard deviation; Mann-Whitney Test: values expressed in mean (Vmin-Vmax).
Source: Azzuz JPRG, et al., 2024.

Table 4 - Indicators of metabolic syndrome in children and adolescents with Down Syndrome attended at the Pediatric Endocrinology outpatient clinic at UFTM, Uberaba-MG.

	Female - n = 10 (%)	Male - n = 10 (%)	Total - n = 20 (%)
Adiposity by BMI Z-score			
Low weight	3 (30)	0 –	3 (15)
Adequate	4 (40)	4 (40)	8 (40)
Risk of obesity	1 (10)	0 –	1 (5)
Overweight	2 (20)	3 (30)	5 (25)
Obesity	0 –	2 (20)	2 (10)
AC increased	1 (10)	2 (20)	3 (15)
NA presence	3 (30)	5 (50)	8 (40)
SAH	0 –	2 (20)	2 (10)
Basal insulin (↑)	2 (20)	5 (50)	7 (35)
HOMA-IR changed	1 (10)	4 (40)	5 (25)
HDL-Cholesterol (↓)	5 (50)	5 (50)	10 (50)
Triglycerides (↑)	7 (70)	5 (50)	12 (60)
Ferritin (↑)	2 (20)	4 (40)	6 (30)

Note: AC: abdominal circumference; AN: acanthosis nigricans; SAH: systemic arterial hypertension; HOMA-IR: Homeostatic Model Assessment - Insulin Resistance.
Source: Azzuz JPRG, et al., 2024

Correlations were made between clinical and laboratory variables and those that were significant at some point are expressed in (**Table 5**). Some data such as TSH and cholesterol concentrations and cholesterol fractions were not correlated with any of the variables and for this reason are not represented.

The clinical variables Z-BMI and AC showed a significant and inverse correlation with Free T4 and Total T3 and direct correlations with basal insulin, ferritin and triglycerides. Other expected direct significant correlations were verified as Glucose with AC, HbA1c, basal insulin, HOMA-IR, triglycerides and ferritin. HbA1c only correlated with triglycerides and glucose.

Table 5 - Correlations between thyroid and cardiometabolic parameters in children and adolescents with Down Syndrome treated at the Pediatric Endocrinology outpatient clinic at UFTM, Uberaba-MG.

	Z-BMI		AC		Glucose		Basal insulin		HOMA-IR		Triglycerides	
	r	p	r	p	r	p	r	p	r	p	r	p
AC	0.668	0.002*	–		0.341	0.140	0.453	0.045*	0.376	0.102	0.448	0.049*
Free T4	-0.438	0.005*	-0.558	0.012*	-0.077	0.743	-0.386	0.092	-0.314	0.175	-0.025	0.913
Total T3	-0.626	0.004*	-0.457	0.004*	-0.107	0.648	-0.403	0.078	-0.363	0.115	-0.279	0.230
Fasting blood glucose	0.341	0.140	0.665	0.002*	–		0.529	0.017*	0.688	0.001*	0.498	0.027*
HbA1c	0.286	0.219	0.352	0.126	0.532	0.017*	0.359	0.119	0.402	0.079	0.631	0.003*
Basal insulin	0.453	0.045*	0.724	0.001*	0.529	0.017*	–		0.965	0.001*	0.570	0.010*
HOMA-IR	0.376	0.102	0.722	0.001*	0.688	0.01*	0.965	0.001*	–		0.167	0.476
Ferritin	0.679	0.001*	0.450	0.043*	0.00	1.00	0.506	0.024*	0.371	0.106	0.167	0.476
Triglycerides	0.436	0.055	0.448	0.048*	0.631	0.010*	0.612	0.005*	0.612	0.005*	–	

Note: Correlação de Sperman *p<0.05; AC: abdominal circumference; HbA1c: glycated hemoglobin; HOMA-IR: Homeostatic Model Assessment - Insulin Resistance.
Source: Azzuz JPRG, et al., 2024.

DISCUSSION

The life expectancy of people with DS has improved considerably in recent decades, being described as 12 years in 1940 to around 60 years today, and this change has been attributed to research into the clinical and surgical treatment of congenital heart disease, as well as treatment of comorbidities such as obesity, sleep apnea, neuropsychiatric, gastrointestinal and endocrine diseases such as diabetes and hypothyroidism (WHOOTEN R, et al., 2018; ANTONARAKIS SE, et al., 2020). Some authors suggested that patients with DS are not preferential targets for atherosclerosis due to overexpression of genes located on chromosome 21, while other ones have shown changes in the autonomic control of the heart, endothelial dysfunction and arrhythmias (SOBEY CG, et al., 2015; SANTORO M, et al., 2018; CILHOROZ BT, et al., 2022; DIMOPOULOS K, et al., 2023).

DS is also characterized by premature aging with a propensity for osteoporosis and Alzheimer's disease (WHOOTEN R, et al., 2018; ANTONARAKIS SE, et al., 2020). Multidisciplinary care are necessary to prevent complications that could shorten the lives of patients with DS and provide them with the autonomy and quality of life (BERTAPELLI F, et al., 2016). With these aspects in mind, the present study is aimed at studying children and adolescents regularly treated and referred due to two main demands: hypothyroidism and overweight/obesity.

We therefore try to analyze the causes of hypothyroidism and whether it is being well treated, the consequences of overweight/obesity and whether there are relationships between both conditions. Regarding hypothyroidism, we observed 2/20 (10%) of CH, with topical and reduced thyroid on ultrasound; 5/20 (25%) due to CAT and the rest of the cases with an etiology not clearly defined but still treated because they were either referred with manifest or subclinical primary hypothyroidism.

CH in DS is 29 to 35 times more frequent than in the general population, and an incidence of 1:113 and 1:410 live births has been reported (AMR NH, 2018) accompanied by congenital malformations of the gastrointestinal and cardiovascular system. Most reports of CH in DS have been attributed to hypoplasia (LUTON D, et al., 2012; AMR NH, 2018). Luton D, et al. (2012) studied 13 thyroids from human fetuses with DS between 23 and 33 weeks of gestation. He observed small thyroids with few follicles that stained poorly on immunohistochemistry with anti-thyroglobulin antibodies, suggesting hypoplasia and immaturity.

Although there are some interesting and plausible hypotheses, CH in DS is still the subject of many investigations (FARIA CD, et al., 2011; IUGHETTI L, et al., 2014; AMR NH, 2018). Regarding CAT, its association with DS is well known, and with other autoimmune diseases such as celiac disease (5-10%), type 1 diabetes (3 times more common) and autoimmune alopecia (11.4%) (AMR NH, 2018). According to Aversa T, et al. (2015) the average age of initiation of CAT in DS would be 6.5 years and in 73.3% before 10 years of age, which indicates the need for early screening. Numerous studies seek to explain the higher incidence of autoimmune diseases in DS, one of the most attractive being mutations in the autoimmune regulatory gene (AIRE) located in 21q22.3.

It is a transcription factor involved in immune regulation and inactivating mutations in this gene may be linked to autoimmune polyendocrine syndrome type 1 (APS1). In the case of DS, its connection to the AIRE gene could occur due to hyperexpression of this gene caused by the presence of an extra copy of chromosome 21 (GIMÉNEZ-BARCONS M, et al., 2014). Other hypotheses to explain autoimmune diseases and SD have been investigated, such as changes in the regulation of pro-inflammatory cytokines, suppressive effects of alpha interferon and its toxic effects on the thyroid (AMR NH, 2018).

The other cases of primary hypothyroidism in the present study, 13/20 (65%), have no defined etiology. It may be that later on the antibodies become positive and a retrospective diagnosis of CAT is made, or it may be that these are developmental anomalies that do not manifest clinically from birth as pathogenic variants of the DUOX2 and DUOXA2 genes (WANG F, et al., 2020). Regardless of the etiology, all patients in the present study had Free T4 and Total T3 values within reference values, although 4 of them had slightly increased TSH values, with individualized doses of L-Thyroxine and regular controls every 4 months in the study period.

The nutritional status was checked by BMI and BMI Z-score (Z-BMI) as is routinely done in the outpatient clinic where they are cared for. The male group had a significantly higher Z-BMI than the female group and in 50% of cases they were overweight/obese. Considering the entire group, 25% were overweight and 10% were obese, such numbers are not greater than those found in children and adolescents in the Brazilian population and in our region (BLOCH KV, et al., 2016; SILVA APD, et al., 2018).

In the literature there are numerous reports of increased prevalence of overweight and obesity in DS, but with great variability. Combining overweight and obesity, the reported prevalence varies from 23-70%, indicating that in some studies it is higher than the general population (BERTAPELLI F, et al., 2016). Furthermore, some authors found a predominance of overweight/obesity in females (GONZÁLEZ-AGÜERO A, et al., 2010). Our findings differ from the literature in that they are patients who already attend the outpatient clinic and have already received nutritional guidance and physical activity, considered beneficial in DS (BERTAPELLI F, et al., 2016).

Among the determining factors of obesity, the literature points out that in DS there would be lower resting energy expenditure (REE), decreased physical activity related to orthopedic problems, inadequate eating patterns and comorbidities such as hypothyroidism, congenital heart defects, difficulties in chewing such as muscular hypotonia of the tongue, incorrect tooth position, esophageal dysmotility and a series of oro-motor difficulties that can affect eating behavior, influencing food choices and selectivity (MOREAU M, et al., 2021).

Other factors are also highlighted, such as poor socioeconomic status, medications for psychiatric diseases associated with weight gain, immaturity of the food intake regulatory center with a reduction in the number of neurons in the arcuate nucleus of the hypothalamus, as well as resistance to leptin, which would be increased in DS (WISNIEWSKI KE e BOBINSKI M, 1991; MAGGE SN, et al., 2008; EL GEBALI HH, et al., 2014; PALUMBO ML e MCDOUGLE CJ, 2018).

Some of the consequences of overweight/obesity were observed in this series, such as increased AC, AN, increased basal insulin, HOMA-IR, reduced HDL-Cholesterol, increased triglycerides and ferritin with higher percentages of abnormalities in males. They are clinical and laboratory markers of insulin resistance that appeared before there were changes in blood glucose and HbA1c. A single patient had type 1 diabetes and was in good control. These parameters, also called cardiometabolic risk, showed positive and significant associations with Z-BMI and AC.

Insulin resistance, metabolic syndrome and T2DM are common in individuals with DS, related to obesity and centripetal fat distribution. According to Magge SN, et al. (2019) fat distribution appears to be more important in the development of T2DM in people with DS than obesity itself. Adipose tissue proliferates more than the vasculature leading to hypoxia, cell apoptosis and inflammation with an increase in pro-inflammatory cytokines such as TNFα involved in the development of insulin resistance before the onset of T2DM (BROERS CJ, et al., 2012). In the present study, insulin concentrations showed positive and significant correlations with ferritin and triglyceride concentrations, which is a condition for the appearance of hepatic steatosis.

According to Valentini D, et al. (2017) there would be a greater risk of developing nonalcoholic fatty liver disease (NAFLD) in individuals with DS and an earlier approach to predisposing factors would be worthwhile. Regarding lipid concentrations, they were significantly higher in the male group compared to the female group in the n-HDL-Chol fractions, indicating higher LDL values in this group. Furthermore, triglyceride concentrations were also higher in males and in both sexes, HDL fractions showed similar percentages of reduction, as demonstrated by other authors (PECORARO L, et al., 2023). As previously mentioned, except for triglyceride concentrations, these variables did not correlate with anthropometric and laboratory variables. It is likely that they express the dietary pattern or other determinants to be investigated.

More recent studies indicate a predisposition to atherosclerosis in patients with DS related to such lipid abnormalities (HETMAN M, et al., 2023). An interesting fact from the present study that draws attention to greater care in relation to the treatment of hypothyroidism in DS was the finding of an inverse and significant correlation between Z-BMI and AC with concentrations of Free T4 and Total T3 (**Table 5**). TSH, in turn, did not correlate with any parameter evaluated. Thyroid hormones, especially T3, act on energy expenditure, especially on basal metabolic rate (BMR), increasing the production of ATP for multiple metabolic processes at the mitochondrial level, modulating appetite and food intake, facilitating adaptive thermogenesis and body weight regulation.

Together with leptin, they regulate signaling to the hypothalamic arcuate nucleus and reflect changes in energy stores (HETMAN M, et al., 2023). Our data also indicate that in DS they interfere with fat distribution because the lower the concentrations of Free T4 and Total T3, the higher the Z-BMI and AC and as a result of increased adiposity, insulin resistance arises (BERTAPELLI F, et al., 2016; PALHARES HMDC, et al., 2018; CILHOROZ BT, et al., 2022). Müllur R, et al. (2014) states that there are numerous pathways to be investigated to integrate the regulatory mechanisms of thyroid hormones and glucose metabolism and insulin signaling pathways.

An alert that such data give rise to is that L-Thyroxine therapy must be optimized in DS by providing adequate levels of Free T4, Total T3 and TSH through careful and frequent determinations. Among the limitations of this research, we can point out the small number of patients who participated in the study and the absence of a control group of patients with DS and without hypothyroidism. We hope to expand and resolve these limitations in future studies.

CONCLUSION

We conclude that as the life expectancy of patients with DS increases, new challenges arise in the search for excellence in their health care and quality of life. The data from the present study indicate the need to optimize the treatment of hypothyroidism, especially in male patients. In relation to metabolic aspects, there must be treatment and prevention of complications that begin at birth and last throughout life, involving multidisciplinary teams, as a result of the needs that patients present throughout their lives.

THANKS AND FUNDING

To the patients who agreed to contribute to the study, and to Fapemig for the grant received by the author João Pedro Rodrigues Guimarães Azzuz.

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