OBESITY AND OVERWEIGHT AND ACCOMPANYING METABOLIC DISORDERS OCCUR IN CHILDREN WITH DOWN SYNDROME

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ABSTRACT

Objective: *To evaluate the prevalence of overweight, obesity, selected metabolic disorders and additional chronic diseases in children with Down syndrome (DS).*

Materials and methods: *The study was conducted in a group of children with DS under the care of the Department of Pediatrics, Hematology and Oncology of the Medical University of Gdansk from May 2017 to December 2018.*

Results: *The study included 26 female patients and 22 male patients with DS, aged 7 to 18 years. The children were divided into two groups: a group with normal body weight and underweight and a group with obesity and overweight. Overweight and obesity were diagnosed in 19% of children with DS. Higher values of HDL cholesterol were found in patients with normal body mass and underweight than in patients with obesity and overweight (p=0.009). Higher values of uric acid were found in the group of patients with obesity and overweight than in the normal mass and underweight group (p=0.012). The children who are physically active have normal body weight (p=0.039).*

Conclusions: *Obesity and overweight in patients with DS are linked to elevated uric acid levels and lipid disorders and the role of salusin-β as an early indicator of metabolic disorders in children with DS was not demonstrated. Due to the incidence of disorders, continuous nursing care, check-ups and continuous health education of families is necessary.*

Keywords: *Obesity, overweight, metabolic disorder, child, Down syndrome, nurse.*

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Introduction

Obesity is a childhood disease of affluence. In recent years, a significant increase in the incidence of overweight and obesity has been observed around the world[(1)]. People with intellectual disabilities are considerably more often exposed to various types of health disorders compared to mentally competent people. Factors that may affect the occurrence of such disorders include sex, age, place of residence, intellectual performance, degree of mental disability, living conditions, diet and eating habits, knowledge about nutrition, physical activity, medications and genetic determinants[(2)]. Overweight or obesity are the main risk factors for hypertension and other cardiovascular diseases, atherosclerosis and type 2 diabetes[(1)]. The treatment of obesity in children with mental disabilities is difficult. The treatment is based on a proper diet, increased physical activity, education and behavioural therapy[(1, 3)].

Educational training can be conducted by a whole therapeutic team, i.e., a nurse, dietician, psychologist, and doctor. The nurse plays an important role in the prevention and treatment of overweight

and obesity in children[1, 3]. School and community nurses play a special role in the care of children with disabilities and their families[3, 4].

Down syndrome (DS) is the most common chromosomal disorder and is associated with congenital heart defects, hearing and vision disorders, thyroid diseases, gastrointestinal disorders, cognitive impairment, intellectual disability, obstructive sleep apnoea, and muscular hypotonia. Characteristic features of people with DS include short stature, small head, single palmar crease, almond-shaped eyes caused by the skin fold of the upper eyelid, and reduced muscle tone. Children with Down syndrome are born with low birth weight, whereas their overweight condition can already be observed at approximately 3-4 years of age[5-7].

Factors that influence the development of obesity and overweight in patients with DS include age, place of residence, national and ethnic factors, physical structure, intellectual performance and the degree of mental disability, lack of ability to correctly diagnose and articulate their nutritional needs, living conditions, diet, eating habits and knowledge about nutrition, physical activity, drug use, social factors and genetic conditions[5-7].

The aim of the study was to evaluate the incidence of selected metabolic disorders in children with DS taking into account the following: obesity and overweight, hypertension, carbohydrate and lipid disorders, kidney function, hyperuricaemia.

Furthermore, the prevalence of additional chronic diseases in the study group was evaluated.

Patients and methods

The research was conducted in a group of 48 children with DS under the care of the Genetic Clinic of the Department of Pediatrics, Hematology and Oncology of the Medical University of Gdansk of the University Clinical Centre in Gdańsk from May 2017 to December 2018. The study included female and male patients with DS aged 7 to 18 years and their parents or legal guardians who gave informed consent to participate in the study. The selection of patients for the study was random.

The exclusion criteria were as follows:

• Patients with DS under 7 years of age and over 18 years of age and a lack of consent from parents or legal guardians to participate in the study.

The research was based on the analysis of the anthropometric data, results of selected laboratory tests and clinical data collected on the basis of the questionnaires completed by parents. Anthropometric measurements were performed on each child. The body weight of children in underwear was measured with AXIS scales (B150L), and the body height was measured with a SECA stadiometer attached to the AXIS scales (year of production 2008).

Percentile charts by Zemel et al. (2015) were used in the assessment of a child's nutritional status[8].

The diagnosis of disorders of nutritional status was based on the current standards for assessment of anthropometric parameters for children with DS, which recommended the diagnosis of overweight and obesity on the basis of the 85th and 95th percentiles (overweight: body mass index BMI ≥85th percentile and <95th percentile; obesity: body mass index BMI ≥95th percentile), underweight <5th percentile[8].

Blood pressure (BP) was measured with a standardized Omron HBP-1100 monitor (year of production 2014).

To measure BP correctly, the width of the cuff was individually selected depending on the circumference of the patient's arm. The measurements were taken 3 times after a 10-minute period of rest in a sitting position on the patient's right arm. The tests were carried out in the morning hours. The average BP values were calculated and compared to the percentile blood pressure values for sex, age and height of American children[9].

The systolic and diastolic pressure values <90th percentile for children aged 1-13 years for both types of BP or for children aged ≥13 years <120/<80 mmHg were considered to be normal BP(9).

Elevated BP for children aged 1-13 years was diagnosed if the values of the systolic and/or diastolic pressure remained ≥ 90th percentile to <95th percentile or 120/80 mmHg to <95th percentile (whichever is lower) and for children aged ≥13 years 120/<80 to 129/<80 mmHg[9].

Hypertension was diagnosed if the systolic and/or diastolic pressure values exceeded the 95th percentile or 130/80 mmHg to 139/89 mmHg (whichever is lower)[9]. Laboratory tests were performed in the Central Laboratory of the University Clinical Centre in Gdansk and in the Department of Clinical Nutrition and Dietetics, in the Department of Clinical Nutrition of the Medical University of Gdansk.

The eGFR value was determined according to Kidney Disease: Improving Global Outcomes (KDIGO) recommendations using the formula eGFR (estimated glomerular filtration rate)=0.413 x body length (cm) / creatinine concentration (mg/dl)[10-13]. Salusin-β concentrations were determined by the im-

munoenzymatic method using Elisa set for salusin-β (produced by Cloud-Clone Corp, 2018) and E-Liza MAT 3000 device.

Glycated haemoglobin (HbA1c) was determined by high-performance liquid chromatography HPLC with the use of Variant II BioRad device; glucose by the enzymatic method; total cholesterol by the method based on a reaction accelerator and a selective detergent; low-density lipoprotein (LDL cholesterol) and high-density lipoprotein (HDL cholesterol) by a direct measurement with the use of a liquid selective detergent; triglycerides (TGs) by glycerol phosphate oxidase and the Architect C8000 device; thyroid hormones, thyroid-stimulating hormone (TSH), free thyroxine (fT4), and free triiodothyronine (fT3) by the chemiluminescent method using the Architect J2000 device; uric acid by a measurement method based on uricase; creatinine by the enzymatic method; and urinary albumin concentration by the immunoturbidimetric method. The urinalysis was assessed with strip tests using an IRIS IQ 200 SPRINT device.

Serum creatinine levels were assayed using an enzymatic method. The estimated glomerular filtration rate was calculated based on creatinine serum levels. The plasma lipid profile was determined by electrophoresis. The concentration of salusin-β was measured using the ELISA method (Cloud-Clone Corp.). GFR was measured indirectly using the original Schwartz formula. The Schwartz formula is defined as follows: GFR in mL/min/1.73 sq m = k x height of child in cm/serum creatinine concentration in mg/dL, where the constant k was defined using the published literature values of k=0.413 for children aged 2-18[10-13].

Lipid values were evaluated according to the guidelines of the American Academy of Pediatrics from 1992[14].

Ethical considerations

The research was approved by the Independent Bioethics Committee for Scientific Research of the Medical University of Gdansk (document number NKBBN/345/2017). The legal guardians completed the questionnaire in a separate room in the hospital outpatient clinic to respect their privacy. To reduce the risk of coercion, all participants were informed that they could withdraw from the study at any time.

Data analysis

The obtained results were subjected to statistical analysis. Continuous parameters are presented as the median (M) and interquartile range (lower and upper quartiles). To verify the hypothesis of the equality of mean parameters in independent groups, the nonparametric Mann-Whitney U test was conducted (the homogeneity of variance was checked with Bartlett's test). For discrete parameters, the frequency of trait occurrence in the groups was analysed with the χ^2 test. $P \leq 0.05$ was considered statistically significant. The statistical analysis was carried out using the statistical software EPIINFO Ver. 7.1.1.14 (02-07-2013).

Results

The study included 48 patients with DS (26 females, 22 males) aged 7 to 18 years. Nutrition disorders were found in 15 patients, including obesity in 2, overweight in 8, and underweight in 6. The examined children were divided into two groups: a group with normal body weight and underweight (81%) and a group with obesity and overweight (19%). The groups were compared with one another.

The analysed groups did not differ in age (p=0.938; Table 1), sex (p=0.164) or place of residence (p=0.640). Among the biochemical parameters that were determined, there were no differences between the groups in fasting glucose levels, glycated haemoglobin, total cholesterol, triglycerides, and LDL cholesterol (Table 2).

	Whole group (n=48)	Normal body weight and underweight (n=39)	Obesity and overweight (n=9)	P
Age [years]	12.0 (9.0÷16.0)	12.0 (9.0÷16.0)	12.0 (11.0÷15.0)	0.938
Body weigh[kg]	37.3 (28.9÷51.5)	33.1 (27.6÷48.0)	58.1 (48.2÷74.5)	0.000
Body height [m]	1.39 (1.24÷1.48)	1.36 (1.23÷1.44)	1.56 (1.42÷1.62)	0.007
BMI**[kg/m²]	19.9 (17.6÷24.1)	18.3 (17.0÷21.9)	24.3 (23.8÷26.3)	0.000

Table 1: Age, body weight and height, BMI in the studied groups.
*Test Mann-Whitney U. *For variables without a normal distribution, the median, 25Q, and 75Q are presented. **BMI, body mass index.*

Abnormal results of fasting glucose were found in 4/48 (8%) of the patients, glycated haemoglobin in none, total cholesterol in 20/48 (42%), HDL cholesterol in 4/48 (8%), LDL cholesterol in 16/48 (33%), TG in 1/48 (2%), uric acid in 14/48 (29%), and eGFR < 90 ml/1.73 m2/24 h in 26/48 (54%), including 2 patients with eGFR <60 ml/1.73 m2/24 h.

Patients with normal body mass and underweight had higher values of HDL cholesterol than patients with overweight and obesity (p=0.009). Higher values of uric acid were found in the group of

patients with obesity and overweight than in the normal weight and underweight group (p=0.012). eGFR did not differ between the groups (p=0.586; Table 2).

	Whole group (n=48)	Normal body weight and underweight (n=39)	Obesity and overweight (n=9)	P
Fasting blood glucose [mg/dl]	88.0 (85.0÷95.0)	87.5 (84.0÷94.0)	94.0 (87.0÷95.0)	0.184
HbA1c** [%]	5.1 (4.90÷5.30)	5.1 (4.9÷5.30)	4.90 (4.90÷5.20)	0.401
Total cholesterol [kg]	164.0 (139.0÷190.0)	165.0 (141.0÷190.0)	163.0 (127.0÷174.0)	0.567
Triglycerides [mg/dl]	71.0 (58.0÷96.0)	69.5 (57.0÷89.0)	74.0 (66.0÷106.0)	0.343
HDL cholesterol** [mg/dl]	48.0 (40.0÷54.0)	50.0 (41.0÷57.0)	42.0 (35.0÷45.0)	0.009
LDL cholesterol** [mg/dl]	100.5 (87.0÷118.0)	100.5 (87.0÷118.0)	104.0 (84.0÷114.0)	0.947
Uric acid in the blood [mg/dl]	5.4 (5.0÷6.5)	5.2 (4.9÷6.0)	6.4 (6.1÷6.9)	0.012
eGFR** [ml/min/ 1.73 m2]	86.6 (77.4÷100.2)	88.2 (77.4÷100.2)	80.9 (79.9÷88.9)	0.586
Salusin β [pg/ml]	123.5 (83.7÷150.4)	124.1 (85.7÷150.4)	121.4 (77.8÷138.7)	0.801
TSH** [μU/ml]	2.00 (1.5÷2.79)	1.95 (1.48÷2.7)	2.34 (1.71÷3.11)	0.497
fT3** [pmol/l]	4.2 (3.85÷4.62)	4.19 (3.88÷4.62)	4.30 (3.84÷4.57)	0.968
fT4** [pmol/l]	13.3 (12.2÷15.2)	13.3 (12.2÷15.4)	13.0 (12.8÷13.7)	0.567

Table 2: Selected laboratory parameters of the metabolic disorders and thyroid hormones in the studied groups.
*test Mann-Whitney U. *For variables without a normal distribution, the median, 25Q, and75Q are presented. **HbA1c, glycated haemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; eGFR, estimated glomerular filtration rate; fT4, free thyroxine; fT3, free triiodothyronine; TSH, thyroid-stimulating hormone.*

No differences in serum concentrations of salusin-β were found between the studied groups (p=0.801), Table 2. The studied groups did not differ in systolic and diastolic BP values (Table 3). No differences in the incidence of normal BP and hypertension were found between the studied groups (p=0.611). Hypertension were found in 29% of patients (Table 4).

	Whole group (n=48)	Normal body weight and underweight (n=39)	Obesity and overweigh (n=9)	P
Systolic BP** [mm Hg]	109.5 (102.5÷117.0)	107.0 (102.0÷115.0)	117.0 (110.0÷117.0)	0.097
Diastolic BP** [mm Hg]	71.5 (64.0÷78.0)	71.0 (64.0÷77.0)	75.0 (70.0÷79.0)	0.659

Table 3: Blood pressure in the studied groups.
*test Mann-Whitney U. *For variables without a normal distribution, the median, 25Q, and 75Q are presented. **BP, blood pressure.*

	Normal body weight and underweight (n=39)		Obesity and overweigh (n=9)		P
	1	2	1	2	
Normal BP*-1 hypertension-2	27	12	7	2	0.611

Table 4: Blood pressure in the studied groups.
*test χ^2. *BP, blood pressure.*

The comparison of TSH, fT3, and fT4 did not show differences between the groups. (Table 2).

Based on the obtained survey data, an attempt was made to determine the influence of various factors on the incidence of obesity and overweight in children with DS. The studied groups were assessed based on a medical history of hypothyroidism and hyperthyroidism, type 1 diabetes, celiac disease and juvenile idiopathic arthritis. No significant differences were found between the groups (Table 5).

The influence of specialist care on the incidence of overweight and obesity in the studied groups was analysed (Table 5). It was shown that children who are physically active have normal body weight (p=0.039). In the group with normal body weight and underweight, 49% of children are under the care of a physiotherapist, while in the group of children with obesity and overweight, only 11% were receiving such care (Table 5).

	Normal body weight and underweight (n=39)		Obesity and overweight (n=9)		P
	1	2	1	2	
The child's additional chronic disease (1 - present, 2 - absent)	26	13	7	2	0.517
Hypothyroidism (1 - present, 2 - absent)	32	7	7	2	0.767
Hyperthyroidism (1 - present, 2 - absent)	1	38	1	8	0.247
Juvenile idiopathic arthritis (1 - present, 2 - absent)	6	33	1	8	0.743
Type 1 diabetes (1 - present, 2 - absent)	5	34	0	9	0.256
Celiac disease (1 - present, 2 - absent)	2	37	0	9	0.488
Dietician's care (1 - yes, 2 - no)	4	35	1	8	0.940
Physiotherapist's care (1 - yes, 2 - no)	19	20	1	8	0.039
Psychologist's care (1 - yes, 2 - no)	22	17	2	7	0.065
Endocrinologist's care (1 - yes, 2 - no)	36	3	9	0	0.390
Diabetologist's care (1 - yes, 2 - no)	4	35	2	7	0.328
Cardiologist's care (1 - yes, 2 - no)	22	17	3	6	0.212
Neurologist's care (1 - yes, 2 - no)	12	27	0	9	0.055

Table 5: The occurrence of additional chronic diseases in the studied groups and supervision of specialist doctors in the studied groups test χ^2.

Discussion

DS is the most common chromosomal disorder, occurring at a frequency ranging from 6.1 to 13.1/ 10,000 people[6, 15]. Children with DS are predisposed to overweight and obesity. According to the literature review prepared by Fabio Bertapelli, the incidence of overweight and obesity in children with DS ranges from 23-70%. Young adults with DS have a higher incidence of overweight and obesity than the general population. It is likely that obesity in children with DS results from increased leptin concentration, reduced energy expenditure, coexistence of other diseases, improper diet and a level of physical activity that is too low. Obesity is related to dyslipidaemia, hyperinsulinemia and gait disorders[6].

The study included 48 Polish children with DS aged 7 to 18 years. The incidence of overweight and obesity was estimated at 19%, and only two patient (4%) was diagnosed with obesity.

These data are closest to the results of the study by Aburavi et al.(16), who assessed a group of 656 Arab children with DS aged 2-16 years and showed that obesity and overweight were diagnosed in 8.8% and 14.2%, respectively, a total of 23%[16].

A significantly higher incidence of obesity is given by other authors: Basil et al.[17] reported an incidence of 47.8% in a group of 303 American children aged 2 to 18 years (total paediatric population 12.1%), Hill et al.[18] reported an incidence of 25% in a group of American children with DS aged 3-10 years, Galli et al.[19] found an incidence of 51.3% in a group of 78 Italian children aged 5-18 years, and Seron, Silva & Gregoul(20) reported an incidence of obesity and overweight of 62% in a group of 41 Brazilian children[17-20].

Brzeziński et al.[21] analysed the data on the prevalence of overweight and obesity among Polish children. They examined a group of 70,329 children aged between 6 and 13 years, divided into groups of girls and boys aged six, seven, nine, eleven and thirteen. They showed that obesity occurred in 1.5-6.8% of seven-year-old boys and 4-7.5% of seven-year-old girls, and overweight occurred in 5.8-6.1% of seven-year-old boys and 11.8-18.4% of seven-year-old girls. In the group of 13-year-olds, overweight was diagnosed in 14.7-20.8% of boys and 15.8-21.5% of girls, and obesity was diagnosed in 2.2-7.1% of boys and 3.7-9.7% of girls[21]. Therefore, it seems that our results in the group of children with DS are comparable to the prevalence of obesity and overweight in the general paediatric population.

In children with DS, cross-sectional studies have the relationship between nutritional status and the levels of total cholesterol (TC), HDL and LDL cholesterol, and triglycerides (TGs). A study conducted by Ordones-Munoz et al.[22] in a group of Spanish young adults with DS aged 16±1 years showed that a higher BMI and waist-to-hip circumference ratio were significantly correlated with higher TC and TG concentrations and lower HDL concentrations[22].

The study conducted by Adelekan et al.[23] found that children with DS aged 4 to 10 years had abnormal lipid profiles regardless of their nutritional status compared to their healthy siblings - these children had significantly higher TC, TG, and LDL and lower HDL levels regardless of race, sex, age, origin and BMI. These studies allow us to conclude that children with DS have a worse (less favourable) lipid profile, and obesity is not as clearly defined as a risk factor for dyslipidaemia in this population[23].

Our studies of children with DS have demonstrated that obese and overweight children have lower HDL cholesterol levels. A significantly higher value of uric acid was also found in comparison with the group of patients with DS with normal body weight and underweight. No statistically significant differences between the groups in fasting glucose, glycated haemoglobin, total cholesterol, LDL and TG or eGFR values were found.

A Japanese study conducted by Niegawa et al.[24], including 102 children with DS aged 5-15 years, showed that obesity and overweight occurred in 14.7% of the subjects, and hypertension occurred in 23.5%[24]. In the group we examined, high values of blood pressure were diagnosed in 31% of patients.

Hyperuricaemia was diagnosed in 23.5% of Japanese children with DS(24), and in our study, 29% of the respondents had a diagnosis of hyperuricaemia. In the Japanese study, hyperuricaemia was defined as uric acid concentrations greater than 6 mg/dl(24), and in our study, hyperuricaemia was defined as concentrations greater than 6.1 mg/dl.

In the examined groups, a significantly higher concentration of uric acid was found in the group of children with obesity and overweight than in the group of children with normal body weight and underweight (p=0.012). Similarly, Aparecida de Miranda et al.[25] showed significantly higher concentrations of uric acid in the group of children with obesity than in the control group[25].

In recent years, salusins, a group of new peptides, have been discovered and found to be involved in lipid metabolism and the development of athero-

sclerosis and arterial hypertension[26, 27]. The concentrations of salusin-β were determined in the examined group. There were no higher concentrations in the group of overweight and obese children than in the normal weight and underweight group.

A Brazilian study of a small group of 15 children aged 10 to 18 years showed that overweight and obese individuals have higher insulin levels and a higher HOMA (homeostasis model assessment) index than children with normal body weight[28]. It is difficult to conclude whether obesity precedes or results from hyperinsulinism in young adults with DS. However, most studies in young adults show that obesity precedes hyperinsulinism[29]. Insulin concentrations were not determined in our study.

Children with DS are a special population group. Body structure determinants affect other norms of anthropometric indices compared to those in the general population. Children with DS have a lower birth weight and grow more slowly than children without DS, and they also have shorter limbs. In most cases, individuals with DS are shorter, and the delay in psychomotor development affects their lifestyle, which can cause obesity and overweight. In the USA, percentile charts for children with DS were developed on the basis of studies of 637 volunteers from 25 states[8]. The American Academy of Pediatrics recommends using percentile charts developed for children with DS to assess their body height and weight and their nutritional status[8]. In the assessment of anthropometric indices, percentile charts for the American population of children with DS were used in our study. Thus far, percentile charts for Polish children with DS have not been developed.

Hypothyroidism is one of the most frequent endocrine disorders occurring in patients with DS. Congenital hypothyroidism is approximately 30 times more common in newborns with DS than in healthy children[30]. Our studies showed that hypothyroidism occurs in 81% of respondents. There were no differences in thyroid hormone levels or in the incidence of thyroid diseases between the studied groups. Children with DS are at a higher risk of autoimmune diseases such as hypothyroidism and hyperthyroidism, juvenile arthritis, type 1 diabetes and celiac disease[31]. In our study, hyperthyroidism was diagnosed in 2/48 patients (4%), adolescent idiopathic joints in 7/48 (14%), type 1 diabetes in 5/48 (10%) and celiac disease in 2/48 (4%). Due to the high incidence of overweight and obesity, abnormal fasting glycaemia, hyperuricaemia, and reduced eGFR, children with DS require special nursing care in the home and school environment, and caregivers and parents need continuous education to prevent and treat the occurrence of disorders.

Limitations

The limitations of the study include the small size of the examined group and the inability to compare the data that was obtained to the population of Polish children with DS. It is commonly known that obesity and overweight are influenced by a variety of factors, including environmental factors, family determinants and lifestyle. Further studies on the causes of the disorders found in the study group are necessary. In conclusion, obesity and overweight in patients with DS are linked to elevated uric acid levels and lipid disorders. Furthermore the role of salusin-β as an early indicator of metabolic disorders in children with DS was not demonstrated. Due to the incidence of disorders, continuous nursing care, check-ups and continuous health education of families is necessary.

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