Clinico-laboratory Diagnostics of the Metabolic Syndrome in the Risk of Cardiovascular Pathology in Children and Adolescents with Obesity

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Abstract: The excess body weight and obesity problems, as well as the metabolic syndrome associated with these conditions, are extremely topical in modern medicine, since they are entailed with the increased risk of cardiovascular diseases, complications, and early disability and reduce life expectancy.
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1. Introduction

Childhood obesity is one of the most serious problems that the world health care systems are facing in the XXI century. The rate of increase in obesity prevalence gives rise to concern. The high prevalence of excess body weight (16% of children in the USA [1]) and obesity (15% in Almaty, Kazakhstan) among the child population (R.B. Bazarbekova et al., 2002) and the risk of formation of metabolic shifts makes the metabolic syndrome (MS) problem in pediatrics particularly important, since this condition frequently remains for one's entire life [2, 3]. Children with excess body weight and obesity are prone to obesity in adulthood; the risk of developing such non-infectious conditions associated with MS as diabetes, cardiovascular diseases, arterial hypertension (AH), carbohydrate metabolism disorder, dyslipidemia, hyperuricemia, microalbuminuria (MAU), and sclerocystosis of ovaries in early age is more likely in these children. Prevalence of MS among children is relatively low (3–4%), whereas 25% of adults within a population have MS [4,5,6,7]. Researchers have recently been focusing on this syndrome. MS is a significant factor of early disability and death. The chronic nature of AH, obesity, and carbohydrate metabolism disorder in individuals with this syndrome can be attributed to the hyperinsulinism condition in these patients, which is caused by insulin resistance (IR). This condition is associated with hormonal and metabolism disorders, causes structural and functional changes in the myocardium and vessels, as well as left ventricular remodeling and hypertrophy [8,9,10].

It is rather topical to study the association between childhood/adolescent obesity and metabolic syndrome and certain changes in the metabolism in children, since this problem is close to predicting a number of adult disorders.

In this connection, early diagnostics of clinical and paraclinical MS markers in children and adolescents is a significant fundamental and practical problem. Solution to this problem will provide a different view of the nature of development of the cardiovascular pathology, elaborating the most efficient methods for therapeutic action in the aspect of early prophylaxis and correction of the increased vascular tone, morphological and functional myocardial changes, and metabolic disorders in this group of children.

The objective of this work was study the clinico-laboratory indicators in children with obesity and metabolic syndrome as predictors of cardiovascular disease.

2. Material and Methods.

The work was based on the data obtained clinical studies (complaints, patient's life history, antropometric data, and arterial pressure indices) in 127 children and adolescents with obesity aged 6–16. The antropometric data were used to calculate the body mass index (BMI) as the ratio between the body weight (kg) and height (m^2). The abdominal fat distribution was assessed according to the waist to

hip ratio (normal values being < 0.8 in girls and < 0.9 in boys).

The carbohydrate metabolism was assessed according to the diagnostic criteria (WHO, 1999) using the standard glucose tolerance test (SGTT). The IR condition was also evaluated using the Homeostasis Model Assessment (the HOMA index) elaborated by D. Matthews, which indirectly shows the degree to which tissues are sensitive to insulin. IR was diagnosed at HOMA > 2.76 [1].

Lipid exchange parameters included measuring total cholesterol (TC) and triglyceride (TG) levels, high-, low-, and very-low-density lipoprotein (HDL, LDL, and VLDL, respectively) levels.

In order to diagnose albumin excretion with urea, all the examined patients were tested for MAU using Micral-Test II test strips.

MS was verified according to the generally accepted diagnostic criteria (WHO, 1998). The main criteria included dysglycemia on an empty stomach and/or disturbed glucose tolerance and/or IR and/or type 2 diabetes mellitus. The additional criteria included AH; increased TC, TG, LDL, and VLDL levels; reduced HDL, abdominal obesity, and MAU. MS was diagnosed only in patients with one main and at least two additional criteria.

3. Results and discussion.

A total of 127 children with different degrees of obesity were examined; the median age was 11.45±0.49 years. The male: female ratio was 55 (46.46%): 68 (53.54%). The median BMI was 26.84±2.21. Obesity was mostly abdominal in 116 (91.34%) children, while the remaining 11 (8.66%) children were characterized by uniform distribution of the subcutaneous fat layer.

IR was revealed in 64 (50.39%) patients examined. IR status and at least 2 additional criteria gave grounds for diagnosing MS in 58 (45.67%) children.

Patients with MS were selected in accordance with 1998 WHO criteria. The prevalence of individual MS components in children with obesity is shown in Table 1.

Depending on either presence or absence of MS, the examined individuals were classified into the following groups: Group 1 – children without MS, n = 69 (54.33%); Group 2 – with MS, n = 58 (45.67%). Both groups were further divided into age subgroups: 6–8 years, 9–12 years, 13–15 years (Table 2).

An analysis of the clinical data revealed that 104 (81.89%) children complained of excess body weight; increased arterial blood pressure – 24 (18.90%), headache– 96 (75.59%), pain in the heart area – 36 (28.35%), exercise-induced shortness of breath – 50 (39.37%), thirst – 43 (33.86%), increased fatigability – 54 (42.52%), hypodynamia – 8 (6.30%), irritability – 13 (10.24%), increased appetite – 74 (58.27%), and nasal hemorrhages – 11 (0.79%).

Table 1. Prevalence of MS components in children with obesity

MS criteria	Absolute number	%
Main:		
Dysglycemia at empty stomach	7	5.51
Disturbed glucose tolerance	7	5.51
Diabetes mellitus	1	0.79
Hyperinsulinemia	45	35.43
High HOMA index	64	50.39
Additional:		
Obesity	127	100
Abdominal fat distribution	116	91.34
Uniform fat distribution	11	8.66
Arterial hypertension	59	46.46
Hypercholesterolemia	36	28.35
Hypertriglyceridemia	11	8.66
Increased LDL level	0	0
Increased VLDL level	25	19.69
Reduced HDL level	1	0.79
Microalbuminuria	35	27.56

Table 2. Age structure of children with obesity and metabolic syndrome

Age subgroups	Group 1 (n=69)		Group 2 (n=58)	
	Abs. number	%	Abs. number	%
6-8 years	12	17.39	4	6.90
9-12 years	35	50.73	28	48.27
13-16 years	22	31.88	26	44.83
Total	69	100	58	100

Examination of the patients' life history revealed an unfavorable perinatal period in 85 (66.93%) children, head injuries in 29 (22.83%) children, and frequent cold-related diseases in 69 (54.33%) children.

Special attention was paid to family history. A total of 73 (57.48%) of the examined children had family history of obesity; 45 (35.43%) children, AH; and 45 (35.43%), type 2 diabetes mellitus. It should be mentioned that the main complaints among children with MS were associated with esthetic appearance (obesity), increased appetite and pain in the heart area, headache, and frequent nasal hemorrhages. The life history of these patients included a more unfavorable perinatal period and head injuries, as well as strong family history of diabetes mellitus (Table 3).

A comparative characterization of the physical development indices revealed that children in all age groups had the upper boundaries of height

or were higher than those of children of the same age by 1–1.5 years (Table 4). The heights of 13–16-year-old children turned out to be significantly higher than group 2 children of the same age ($p<0.05$). The median BMI values also attested to obesity; they were significantly higher in group 2 children aged 9–12 ($p<0.02$).

Table 3.Clinical characterization of children

Indicators	Group 1		Group 2	
	Absolute number (n=69)	%	Absolute number (n=58)	%
Complaints				
Excess body weight	56	81.16	48	82.76
Increased appetite	36	52.17	38	65.52
High blood pressure	13	18.84	11	18.97
Headaches	46	66.67	50	86.21
Cardialgia	18	26.07	18	31.03
Shortness of breath	27	39.13	23	39.66
Fatigability	31	44.93	23	39.66
Thirst	25	36.23	18	31.03
Hypodynamia	4	5.80	4	6.90
Irritability	8	11.59	5	8.65
Nasal hemorrhages	5	7.25	6	10.34
Family history:				
Obesity	40	57.97	33	56.90
AH	28	40.58	17	29.31
Diabetes mellitus	23	33.33	22	37.93
Life history:				
Unfavorable perinatal period	40	57.97	45	77.59
Head injuries	12	17.39	17	29.31
Frequent cold-related diseases	38	55.07	31	53.45

Table 4. Characterization of the physical development indices

	Age, years	Median age, years	Height, cm	Body weight, kg	BMI	Chest/Hips
Group 1 (n=69)	6-8	7.0 ± 0.28	129.50 ± 4.87	36.13 ± 2.04	22.49 ± 0.69	0.95 ± 0.01
	9-12	10.74 ± 0.19	150.53 ± 1.66	55.68 ± 1.89	24.37 ±0.5	0.95 ± 0.01***
	13-16	14.0 ± 0.16	166.11 ± 1.51*	83.64 ± 3.75	30.67 ± 1.47	0.90 ± 0.02
Group 2 (n=58)	6-8	7.75 ± 0.25	133.75 ± 3.68	44.55 ± 4.98	24.66 ± 1.43	0.99 ± 0.05
	9-12	10.71 ± 0.22	150.82 ± 2.0	61.43 ± 3.14	26.53 ±0.77**	0.91 ± 0.01
	13-16	13.65 ± 0.11	164.35 ± 1.61	79.92 ± 2.47	29.60 ± 0.72	0.92 ± 0.02

Note: asterisk denotes significant intergroup differences (* – $p<0.05$; ** – $p<0.02$; * – $p<0.001$).**

Examination of the prevalence of clinical indicators of MS (abdominal obesity, AH) in the analyzed groups demonstrates that 91.38% of children in the group with MS had abdominal obesity; the prevalence of abdominal obesity increased proportionally to the age (Fig. 1). The high prevalence of AH among children and adolescents with MS and its dependence on age, which is considerably higher than that among children without MS, comes under notice (Fig. 2).

A thorough study of the carbohydrate metabolism has revealed that dysglycemia on an empty stomach and disturbed glucose tolerance were 1.5 times more prevalent among group 2 children and adolescents (6.90%) compared to group 1 ones (4.35%). Type 2 diabetes mellitus was found in 1 case (1.72%) among children with MS. The prevalence of hyperinsulinemia was considerably higher in group 2 (71.14%) compared to that in group 1 (2.90%). The high HOMA index was above the normal value in 6 (8.70%) children in group 1, whereas being 100% in group 2 children (58 children).

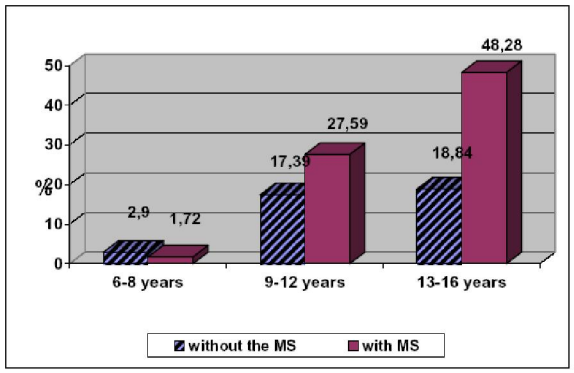

Fig. 1. Prevalence of AH depending on age.

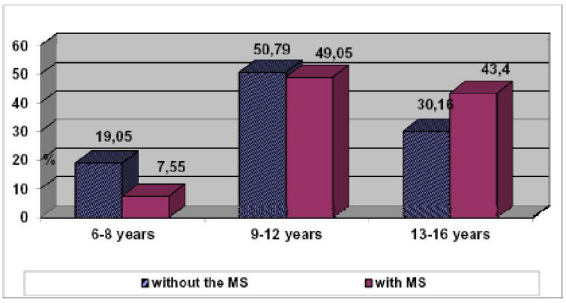

Fig. 2. Prevalence of abdominal obesity depending on age.

The median glucose levels associated with glycemic load were within the acceptable limits in both groups. The median glycemic index on an empty stomach was reliably higher in group 2 children aged 9–12 years; no significant differences were revealed in the remaining cases. The median immunoreactive insulin (IRI) level and HOMA index in children with MS were reliably higher compared to those in children without MS (Table 5).

Table 5. Carbohydrate metabolism indices

Group	Age, years	SGTT (mmol/l)		IRI, μME/l	HOMA
		on an empty stomach	2 h later		
1 (n=69)	6-8	4.17±0.3	4.53±0.48	14.18±0.33	2.30±0.53
	9-12	4.45±0.13	5.22±0.16	10.60±1.40	2.06±0.25
	13-16	4.49±0.15	5.46±0.31	10.12±1.03	1.99±0.18
2 (n=58)	6-8	5.03±0.34	6.05±0.69	68.90±18.89**	14.87±4.17**
	9-12	4.80±0.10	5.61±0.28*	44.08±9.06***	9.55±0.11***
	13-16	4.85±0.14	5.34±0.21	56.45±8.55***	12.03±1.91***

Note: asterisk denotes significant intergroup differences (* – $p<0.05$; ** – $p<0.02$; * – $p<0.001$).**

Among the lipid metabolism indices determined, the CS level was higher in 17 (24.64%) group 1 children and in 19 (32.76%) group 2 children. TG level was higher in 2 (2.90%) group 1 children and 9 (15.52%) group 2 children. In the lipid

metabolism profile, the LDL were within the acceptable normal values; however, the VLDL level was higher in 9 (13.04%) group 1 children and 16 (27.59%) group 2 children; a decrease in HDL was revealed in 1 (1.72%) child with MS.

The median indicators of lipid metabolism profile lied within the acceptable normal values (Table 6). However, an analysis showed that the median TG level in 9–12-year-old children with MS was significantly higher than that in children of the same age without MS ($p<0.05$). A significant decrease in the median HDL level in older age groups (9–12 years, 13–16 years) of children with MS was observed ($p<0.02$; $p<0.001$).

Table 6. Lipid metabolism indices.

Group	Age, years	CS, mmol/l	TG, mmol/l	LDL,%	VLDL,%	HDL,%
1 (n=69)	6-8	4.49±0.29	1.18±0.09	48.39±1.90	21.56±1.53	30.24±2.07
	9-12	4.58±0.12	1.10±0.09	45.50±1.37	20.56±0.16	31.47±1.28
	13-16	4.25±0.16	1.15±0.10	45.35±2.00	20.25±2.10	31.45±0.26
2 (n=58)	6-8	5.09±0.47	1.66±0.65	50.31±3.22	16.98±2.23	32.07±3.26
	9-12	4.82±0.17	1.51±0.16*	49.05±1.58	22.10±1.64	27.27±1.76*
	13-16	4.21±0.15	1.36±0.19	45.97±1.67	24.05±1.70	27.62±1.57**

Note: asterisk denotes significant intergroup differences (* – $p<0.05$; ** – $p<0.02$).

The prevalence rate of MAU in both groups was almost identical: 19 (27.54%) and 16 (27.57%) in groups 1 and 2, respectively. The median MAU values were below 20 μg/l and were not significant in both groups.

When summarizing the resulting metabolic indices, one should mention that the median metabolic indices lied within the normal values; however, an individual examination revealed that these indices are more likely to be disturbed in children with MS. These changes undoubtedly are predictors of cardiovascular pathology.

Arterial blood pressure is one of the hemodynamic indices of the cardiovascular system (CVS). AH was observed in 27 (39.13%) and 32 (55.17%) cases among group 1 and group 2 children, respectively. The increase in SBP within the normal values acceptable for a certain age was observed in 27 (39.13%) and 31 (53.45%) cases in groups 1 and 2, respectively. The minimal blood pressure values allowed one to reveal an increase in DBP in 17 (24.64%) and 22 (37.93%) cases for group 1 and 2 children, respectively. As one can see in Figs. 3 and 4, the prevalence of increased SBP and DBP increases with age in both groups; however, increased blood pressure is more typical of children with MS.

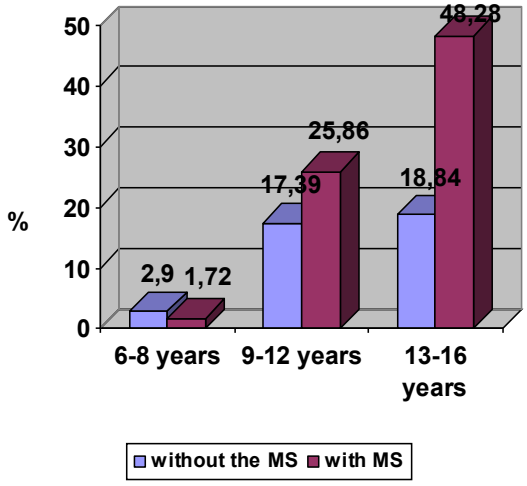

Fig. 3. Characterization of the SBP level depending on age.

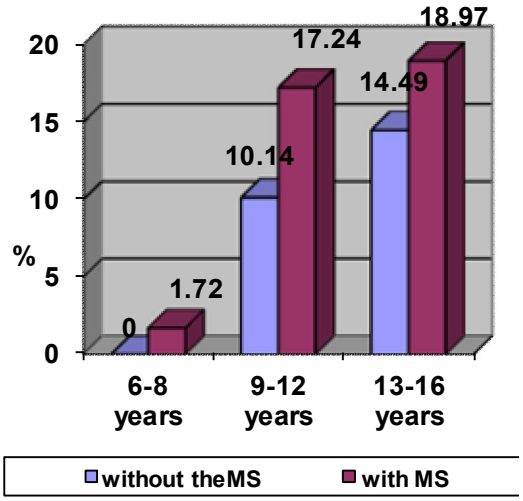

Fig. 4. Characterization of the DBP level depending on age.

An analysis of the median SBP and DBP values shows a tendency towards increased pressure with age; the blood pressure values tended to increase in the oldest age group. The DBP level was reliably higher in 9–12-year-old patients with MS (Table 7).

Tachycardia was detected in 70 (55.12%) children with obesity. The increased HRF was observed in 29 (42.03%) examined children without MS and in 41 (70.69%) of children with MS. An analysis of the median HRF indices revealed tachycardia in all age groups of children with MS, while children without MS showed no tachycardia. However, a comparative assessment of the median values between the groups showed no significant differences for HRF (Table 7).

Table 7. Functional CVS indices depending on age

Group	Age, years	SPB, mm Hg	DBP, mm Hg	HRF
1 (n=69)	6-8	101.0±3.06	65.42±2.98	91.83±2.66
	9-12	113.06±1.99	73.0±1.73	86.71±1.49
	13-16	127.73±3.45	83.41±2.09	85.91±1.98
2 (n=58)	6-8	107.50±4.79	71.25±2.44	93.0±5.26
	9-12	120.14±3.41	79.64±2.66*	90.21±1.80
	13-16	128.88±3.09	84.42±2.24	90.88±1.93

Note: asterisk denotes significant intergroup differences (* – p<0.02).

4. Summary.

The IR status and related metabolic disorders affect the development of functional changes in the CVS in children with obesity and MS.

The IR and GI status in children with MS cause hypervolemia, increased cardiac output, and proliferation of vascular smooth muscle cells, which subsequently causes a spasm, peripheral vascular stenosis, and increase the total peripheral vascular resistance (TPVR). In turn, increased TPVR increases myocardial pre- and postload, left ventricular dilatation followed by left atrial dilation. This was also verified by studies conducted by J.V. Gardin et al. (1987) who emphasized that in addition to body weight, the blood pressure level and activation of various hormones also play a significant role in left ventricular hypertrophy. The aforementioned factors have a synergistic effect on myocardial remodeling. Activation of the sympathetic nervous system, renin-angiotensin-aldosterone system, and GI stimulating the hyperproliferative processes are the most significant humoral factors that stimulate the growth of cardiomyocytes and myocardial fibroblasts (E.I. Sokolov and O.S. Zaichikova, 1996; D.A. Anichkov and N.A. Shostak, 2004; A.S. Ametov, T.Yu. Demidova and L.V. Smagina, 2004).

Obesity and AH have an undoubted effect on the morphological and functional status of myocardium. However, these nosologies are classified as a single syndrome and their combination with other MS components has a stronger effect on the functional and morphological changes in cardiac parameters and development of the CVS pathology (Fig. 5).

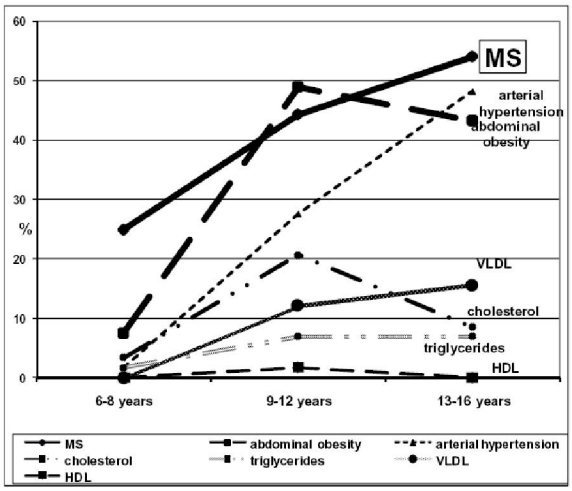

Fig. 5. Age-related risk factors for cardiovascular pathology in children with metabolic syndrome.

5. Conclusions

1. 45.7% of children and adolescents with obesity had a risk of developing metabolic syndrome. The prevalence of MS components tends to increase with age, thus considerably contributing to the development of cardiovascular pathology in adulthood.

2. Insulin resistance and associated neurohumoral disorders promote the development of arterial hypertension in 48.3% of children with metabolic syndrome.

3. Metabolic disorders associated with insulin resistance (disturbed carbohydrate and lipid metabolism) are observed. Such conditions as hyperinsulinemia ($p<0.001$), hypercholesterolemia, hypertriglyceridemia ($p<0.05$), increased VLDL and reduced HDL levels ($p<0.02$) are observed in children with metabolic syndrome.

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