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Research Article

Clinical and Pathogenetic Relationships between the Functional State of the Liver and the Development of Metabolic Syndrome in Children with Obesity

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Abstract

Introduction: There is a high frequency of combination of obesity and liver damage.

Objective: To study the functional state of the liver in children with MS.

Methods: 483 children with obesity (SDS BMI ≥ 2.0) (285 boys and 198 girls) aged 5 to 16 years were examined: the I group - 237 children with MS, the II group - 246 children with obesity without MS. The III group (control) - 30 children with normal body weight. Anthropometry, laboratory and instrumental examinations were carried out.

Results: Ultrasound signs of NAFLD were detected in the I group (70%) and in the II group (51%) ($p < 0.05$) and were not registered in the III group. 91% of children with NAFLD are adolescents of 10-16 years. Boys - 58%, girls - 42%. Abdominal circumference in children with NAFLD was greater than without it (102.5 ± 12.8 cm and 92.3 ± 12.4 cm, $p < 0.05$). ALT increase was found in the I group - 27% and in the II group - 18% ($p < 0.05$). Increased ALT levels were more common in boys than in girls (26% and 13%, $p < 0.05$). Patients with NAFLD were diagnosed with an increase in TG and decrease in HDL, which is more often than children without it. Children with NAFLD had higher levels of insulin, C-peptide and index HOMA-IR. Hyperuricemia was diagnosed in 68% of children with NAFLD and 24% without it ($p < 0.05$), hyperfibrinogenemia - in 28% and 7% ($p < 0.05$), more often in the I group.

Conclusions: 1. Ultrasound criteria for NAFLD among children with MS is diagnosed more often than in children without it (70% and 51%). 2. Adolescents (91%) and males (58%) predominate among children with NAFLD. 3. Abdominal circumference in children with NAFLD is significantly greater than in children without it. 4. Increase of ALT level in children with NAFLD and MS is recorded significantly more often, which may indicate the development of the inflammatory process in the liver. Among patients with hyperfermentemia males predominate (60%). 5. Increased levels of TG and decreased HDL in children with NAFLD are more common than in children without it, and their combination is only in children with MS. 6. More pronounced changes in carbohydrate metabolism are observed in children with NAFLD and MS. 7. NAFLD in children with MS is associated with hyperuricemia and hyperfibrinogenemia.

Keywords: *Children; Obesity; Liver; Non-Alcoholic Fatty Liver Disease; Metabolic Syndrome*

Abbreviations

NAFLD: Non-Alcoholic Fatty Liver Disease; MS: Metabolic Syndrome; ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; PhAl: Alkaline Phosphatase; γ-GTP: Gamma Glutamyl Transpeptidase; Bil: Total Bilirubin; Chol: Total Cholesterol; LDL: Low Density Lipoprotein; HDL: High Density Lipoprotein; TG: Triglyceride

Introduction

Obesity is one of the most urgent medical and social problems of modern health care. In many civilized countries of the world, the number of overweight and obese children tends to increase. The attention of the researchers is draw to the metabolic syndrome (MS) (insulin resistance syndrome) is a symptom complex that combines various metabolic disorders and conditions associated with obesity, single pathogenetic mechanisms based on insulin resistance. Due to the fact that the formation of a complex of symptoms begins in childhood and is asymptomatic for a long time, MS is recognized as an urgent pediatric problem. According to a number of authors, the signs of MS are diagnosed in 30 - 49% of adolescents with obesity [1,2]. There is a high frequency of combination of obesity with NAFLD [3,4]. One of the reasons for the formation of NAFLD is insulin resistance [5]. Different mediators (TNF-α, TGF-β1, IL-6, etc.) are actively secreted in adipose tissue and regulate the sensitivity of insulin receptors. TNF-α activates the Kappa-kinase-beta inhibitor (IKKβ) in adipocytes and hepatocytes. This leads to a violation of insulin binding to the receptor. The effect of TNF-α on insulin receptor type I (IRS-1) is manifest in its phosphorylation, which reduces its tropicity to insulin, reduces the amount of transport protein GLUT-4, which enters glucose into the cell. The decrease in mitochondrial β-oxidation in the liver is associated with a slowdown in the production of transcription factor (PPAR-α) in adipose tissue, which is typical for obesity. In healthy people, the transcription factor PPAR-α is activate by binding to long-chain fatty acids and increases the formation of enzymes oxidative breakdown of fatty acids and mitochondrial transport protein [6]. The development of chronic inflammation in the liver parenchyma is closely associated with the phenomenon of "lipotoxicity". An increase in the concentration of free fatty acids in the blood serum due to persistent lipolysis and lipid peroxidation is consider one of the reasons for the transformation of fatty liver infiltration (steatosis) into nonalcoholic steatohepatitis [7].

Objective of the Study

To study the features of the functional state of the liver in children with MS.

Materials and Methods

483 children with different forms and degrees of obesity (SDS BMI ≥ 2.0) (285 boys and 198 girls) aged 5 to 16 years were examined. The I group consisted of 237 children with obesity complicated by MS, the II group - 246 children with obesity without signs of MS. MS was diagnosed on the basis of IDF criteria [8]. The III group (control)- 30 children with normal body weight of the appropriate age and sex. Comprehensive examination included anamnesis, anthropometry, clinical blood tests, biochemical study of blood serum, lipid spectrum, ultrasound examination of the abdominal cavity, computed tomography.

Results and Discussion

Ultrasound signs of NAFLD were diagnosed exclusively in children of the I and II groups, and in the I group significantly more often than in the II group (70% and 51%, $p < 0.05$). This was manifested in the form of the increased echogenicity of the parenchyma, its diffuse inhomogeneity, vagueness of the vascular pattern and attenuation of the ultrasonic beam. The results of computed tomography showed that in all children the structure of the parenchyma was heterogeneous, the densitometric density of unchanged areas ranged from 55 to 60 Ed H. and the density of individual foci in the native phase ranged from 15 to 43 Ed H. When using the pulse sequence SPAIR (with fat suppression) hypodens areas had a low signal. In all phases of contrast enhancement, including delayed scanning, their density in contrast to the areas with unchanged parenchyma changed slightly. The absolute majority of children (91%) were adolescents of 10 - 16 years, only 9% children - under the age of 10 years, and 23% of them were under 7 years. The findings suggest that the pathological processes in the liver begin long before the clinical manifestation of MS and can be factors in the development and progression of hormonal and metabolic disorders in older age. There were more boys than girls among children with NAFLD - 58% and 42% ($p < 0.05$).

Abdominal circumference in children with NAFLD was greater than without it -102.47 ± 12.77 cm and 92.30 ± 12.36 cm respectively ($p < 0.05$), which may be a confirmation of the close relationship of NAFLD with abdominal obesity, which is considered as the main component of MS.

Increased ALT levels were recorded 37% children with NAFLD, and in the I group significantly more often than in II group (27% and 18%, $p < 0.05$). In 13% and 6% of children of the I and II groups, respectively, the values exceeded the normative indicators by 1.5 or more times, which may indicate the development of the inflammatory process in the liver parenchyma by type of steatohepatitis. Patients with hyperfermentemia were dominated by males (60% of boys and 40% of girls, $p < 0.05$).

A more pronounced increase in the level of markers of cytolytic and cholestatic syndrome in children with NAFLD regardless of the group was detected (Table 1).

	I group		II group		p
	(1) No NAFLD	(2) NAFLD	(3) No NAFLD	(4) NAFLD	
ALT (U/l)	25,0 (20,0 - 39,0)	28,0 (20,0 - 49,0)	18,0 (15,0 - 21,0)	30,0 (23,0 - 42,0)	p1 - 3 < 0,05 p3 - 4 < 0,05
AST (U/l)	26,0 (23,0 - 30,0)	28,0 (21,0 - 39,0)	18,0 (15,0 - 21,0)	29,4 (25,0 - 36,0)	p1 - 3 < 0,05
PhAl (U/l)	194,0 (124,0 - 248,0)	243,0 (167,0 - 322,0)	245,0 (181,0 - 317,0)	254,0 (208,0 - 348,0)	p1 - 2 < 0,05 p1 - 3 < 0,05
γ - GTP (U/l)	18,5 (17,0 - 21,0)	25,0 (17,0 - 32,8)	18,5 (15,0 - 22,6)	22,5 (17,0 - 27,0)	p1 - 2 < 0,05
Bil (mkmol/l)	12,0 (10,0 - 16,3)	12,9 (10,0 - 16,8)	12,0 (10,0 - 17,3)	10,0 (9,7 - 15,0)	p2 - 4 < 0,05

Table 1: *Biochemical indices of blood serum in children (Me, LQ-UQ).*

Increased TG levels in patients with NAFLD were significantly more frequently diagnosed than in children without it (33% of children in the I group and 16% of children in the II group, $p < 0.05$). Reduction of HDL levels had 41% children with NAFLD and only 27% children without it. In contrast to the II group where hypertriglyceridemia and Hypo-alpha-lipoproteinemia were recorded most often separately, in the I group, 29% of children with NAFLD, and 23% of children without it was noted a combination of both.

There were no statistically significant differences between the mean values of plasma lipids within the groups depending on the state of the liver, although there was a tendency to decrease HDL cholesterol and increase TG in children with NAFLD (Table 2).

Indicator	I group		II group		p
	(1) No NAFLD	(2) NAFLD	(3) No NAFLD	(4) NAFLD	
Chol (mmol/l)	4,67 ± 0,97	4,64 ± 0,83	4,86 ± 0,90	4,61 ± 0,76	> 0,05
LDL (mmol/l)	2,99 ± 0,94	2,78 ± 0,70	2,83 ± 0,60	2,70 ± 0,62	> 0,05
HDL (mmol/l)	1,12 ± 0,23	1,11 ± 0,34	1,24 ± 0,26	1,23 ± 0,23	p1-3 < 0,05 p2-4 < 0,05
TG (mmol/l)	1,49 ± 0,53	1,65 ± 0,63	1,15 ± 0,35	1,17 ± 0,36	p1-3 < 0,05 p2-4 < 0,05

Table 2: *Indicators of serum lipidogram in children, depending on the presence of NAFLD (M ± m).*

Regardless of the group, the levels of insulin, C-peptide, and Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) in children with NAFLD were significantly higher than in children without steatosis, indicating more pronounced carbohydrate metabolism disorders in these patients. The most significant differences were in glucose after oral loading: after 1 hour glucose level in children of the I group with NAFLD was significantly higher not only in comparison with children of the II group, but also in comparison with children of the same group without steatosis ($p < 0.05$). The increase of glucose level of the blood serum in the I group was observed with the same

frequency regardless of the state of the liver (68% of children without NAFLD and 69% of children with NAFLD). In the II group hyperglycemia were more often registered in the presence of NAFLD (20% and 8%). This confirms the close relationship with the state of the hepatic metabolism with the formation of MS and impaired glucose metabolism in children (Table 3).

Indicator	I group		II group		p
	(1) No NAFLD	(2) NAFLD	(3) No NAFLD	(4) NAFLD	
Insulin (pmol/l)	146,28 ± 61,19	203,43 ± 108,31	82,27 ± 83,13	86,13 ± 42,0	p1-2 < 0,05 p1-3 < 0,05 p2-4 < 0,05
C-peptide (ng/ml)	3,42 ± 1,32	4,05 ± 1,42	1,78 ± 1,10	2,23 ± 1,04	p1-2 < 0,05 p1-3 < 0,05 p2-4 < 0,05 p3-4 < 0,05
HOMA-IR (Ed)	5,08 ± 2,10	7,03 ± 3,89	2,13 ± 0,71	2,05 ± 1,29	p1-2 < 0,05 p1-3 < 0,05 p2-4 < 0,05 p3-4 < 0,05
Fasting glucose (mmol/l)	5,62 ± 0,78	5,66 ± 0,77	5,06 ± 0,54	4,99 ± 0,52	p1-3 < 0,05 p2-4 < 0,05
Glucose after 1 hour (mmol/l)	6,83 ± 1,85	8,05 ± 2,54	6,67 ± 3,0	6,48 ± 0,98	p1-2 < 0,05 p2-4 < 0,05
Glucose after 2 hour (mmol/l)	5,93 ± 1,23	6,78 ± 1,99	5,10 ± 0,91	6,56 ± 2,57	p1-2 < 0,05 p3-4 < 0,05

Table 3: *Indicators of carbohydrate metabolism in children, depending on the presence of NAFLD (M ± m).*

The relationship of hyperuricemia and hyperfibrinogenemia with the state of the liver were established. Hyperuricemia was diagnosed in 68% children with NAFLD and only in 24% without it ($p < 0.05$), hyperfibrinogenemia - in 28% and 7% children, respectively ($p < 0.05$). Levels of uric acid and fibrinogen in group 1 patients with NAFLD were significantly higher (Table 4).

	I group		II group		p
	(1) No NAFLD	(2) NAFLD	(3) No NAFLD	(4) NAFLD	
Uric acid (mmol/l)	406,0 ± 69,61	421,66 ± 90,55	314,95 ± 75,79	351,17 ± 84,61	p1-3 < 0,05 p2-4 < 0,05 p3-4 < 0,05
Fibrinogen (ng/ml)	3,53 ± 0,54	4,05 ± 0,79	3,80 ± 0,68	3,89 ± 0,53	p1-2 < 0,05 p1-3 < 0,05

Table 4: *Mean values of uric acid and fibrinogen in children with nonalcoholic fatty liver disease (M ± m).*

A comparative analysis of the frequency of NAFLD and ALT levels depending on the state of carbohydrate, lipid and purine metabolism carried out (Table 5).

Indicator	Value in the presence of a trait	Value in the absence of a trait	p
Hyperglycemia			
NAFLD (abs, %)	147 (76,2)	144 (49,6)	< 0,05
ALT (units/l)	26,0 (17,0 - 43,0)	25,0 (18,0 - 36,0)	> 0,05
Dyslipidemia			
NAFLD (abs, %)	219 (66,8)	72 (46,5)	< 0,05
ALT (units/l)	28,0 (20,5 - 39,0)	22,0 (16,0 - 35,0)	< 0,05
Hyperuricemia			
NAFLD (abs, %)	203 (69,8)	81 (42,1)	< 0,05
ALT (units/l)	30,0 (20,0 - 50,0)	20,5 (16,5 - 28,5)	< 0,05

Table 5: *The frequency of nonalcoholic fatty liver disease and ALT level depending on the type of disturbed metabolism (Me, LQ-UQ).*

The frequency of NAFLD and ALT levels were significantly higher in lipid and purine metabolism disorders. This indicates the relationship of these types of metabolic disorders with the degree of severity of the inflammatory process in the liver.

Conclusion

1. Ultrasound criteria for NAFLD in children with MS is diagnosed more often than in children with obesity without MS (70% and 51% respectively).
2. Adolescents (91%) and males (58%) predominate among children with NAFLD.
3. Abdominal circumference in children with NAFLD is significantly greater than in children without it. This indicates a close relationship of functional disorders of the liver with the development and progression of abdominal obesity, which are the main component of MS.
4. Increase of ALT level in children with NAFLD is recorded significantly more often, in children with MS significantly more often than without it (27% and 18%), which may indicate the development of the inflammatory process in the liver parenchyma by the type of steatohepatitis. Among patients with hyperfermentemia males predominate (60%).
5. Lipid metabolism disorders in the form of increased levels of TG and decreased HDL in children with NAFLD are more common than in children without it, and their combination is only in children with MS.
6. More pronounced changes in carbohydrate metabolism are observed in children with NAFLD. The most pronounced changes are recorded in patients with MS.
7. NAFLD in children with MS is associated with hyperuricemia and hyperfibrinogenemia.

Conflict of Interest

No financial interest or any conflict of interest exists.

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