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Metabolic-associated fatty liver disease in children with obesity: a pediatrician's perspective

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Objective — to investigate the characteristics of the development and course of metabolic-associated fatty liver disease (MAFLD) in children with obesity.

Materials and methods. A total of 64 children with obesity aged 11—17 years were examined. The main group included 31 children with obesity and MAFLD; the comparison group comprised 33 children with obesity without MAFLD; and the control group consisted of 34 children matched for age and sex who had neither obesity nor disorders of carbohydrate metabolism. The clinical and laboratory assessment included medical history taking, physical examination, and biochemical blood analysis with measurement of glucose, cholesterol, β-lipoproteins, total bilirubin, thymol test results, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels, the ALT/AST ratio, the de Ritis ratio (AST/ALT), and the Hepatic Steatosis Index. The presence and severity of insulin resistance were assessed using the HOMA-IR index and the Caro coefficient, respectively. Serum insulin, leptin, adiponectin, osteopontin, resistin, and aldosterone levels were measured using commercially available enzyme-linked immunosorbent assay (ELISA) kits. Statistical analysis was performed using the licensed software packages Statistica for Windows 13.0 and SPSS 23.0 for Windows.

Results and discussion. Children with MAFLD were characterized by abdominal obesity, accompanied by decreased de Ritis and Caro ratios and increased ALT/AST ratio, Hepatic Steatosis Index, and HOMA-IR index ($p < 0.05$). Inchildren with MAFLD, serum insulin and aldosterone levels were significantly higher ($p < 0.05$), whereas in children with obesity without MAFLD, the levels of these hormones were within the range observed in the control group. Obesity in children was associated with significantly higher serum osteopontin and leptin levels and lower adiponectin levels, with the most pronounced changes observed in the group with MAFLD ($p < 0.01$). Serum resistin levels were elevated in both groups of children with obesity ($p < 0.05$) and were not associated with the presence of MAFLD. The observed changes in adipokine levels were most pronounced in children with signs of insulin resistance. Based on the findings, a schematic representation of the pathogenetic mechanisms underlying the development of MAFLD in children with obesity was developed.

Conclusions. The development of MAFLD in the setting of obesity is a factor that aggravates the course of the underlying disease and is characterized by abdominal obesity, hyperlipidemia, insulin resistance, and hepatic steatosis. These changes are accompanied by hormonal disturbances, including hyperaldosteronism and hyperinsulinism, as well as increased serum levels of osteopontin and leptin and a simultaneous decrease in adiponectin levels ($p < 0.05$), whereas serum resistin levels remain unchanged. The findings provide a basis for developing measures aimed at preventing the development of MAFLD in children with obesity and ensuring timely treatment of this complication.

Keywords: obesity, metabolic-associated fatty liver disease, insulin resistance, adipokines, children.

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Obesity is a global public health problem: it is estimated that approximately 1.5 billion adults worldwide are overweight, of whom around 500 million are obese [39]. Even more concerning are the rising trends in the prevalence of obesity among children and adolescents, leading to adverse consequences for both physical and mental health [40]. The obesity epidemic is closely linked to the increasing prevalence and severity of metabolic-associated fatty liver disease (MAFLD) [30]. Metabolic-associated fatty liver disease has now become one of the main causes of chronic liver disease worldwide, with a prevalence of 25—37 % in the general population, rising to 90 % in patients with morbid obesity [17]. The pathophysiology of MAFLD and its progression are influenced by many factors. It has been demonstrated that the liver interacts closely with adipose tissue [32], which is not only an energy storage organ but also an endocrine organ that secretes adipokines [4]. There is growing evidence that changes in adipokines occurring during the expansion of adipose tissue contribute to the development and progression of MAFLD through their involvement in the low-grade inflammation that develops in this condition [4, 35]. Despite the numerous studies devoted to this issue, a significant number of questions remain unresolved, which calls for further research in this area. A better understanding of the pathogenic mechanisms underlying the development of MAFLD in children will facilitate the development of therapeutic tools aimed at preventing its onset and enabling early treatment.

Objective — to investigate the characteristics of the development and progression of metabolic-associated fatty liver disease in children with obesity.

Materials and methods

A study examined 64 obese children aged 11—17 years (mean age 13.4 ± 0.3 years). Obesity in children was diagnosed based on body mass index (BMI) calculations. The presence of obesity was assessed using a body mass index (BMI in kg/m^2) exceeding the 97th percentile, in accordance with WHO recommendations [38]. The type of fat distribution was analyzed using the waist-to-hip ratio (WHR) and the waist-to-height ratio (WHtR). Waist circumference (WC) and hip circumference (HC) were measured, and the resulting values were compared with percentile tables [25, 41]. Abdominal (android) obesity was diagnosed in patients with a waist circumference exceeding the 90th percentile for their age and sex. Verification of the MAFLD diagnosis followed the guidelines of the European and North American Societies for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN, NASPGHAN) [32, 37].

The main observation group comprised 31 obese children with MAFLD. The comparison group consisted of 33 obese children without MAFLD. The control group comprised 34 adolescents who were neither overweight nor obese and who, at the time of the examination, presented no signs of MAFLD or intercurrent diseases. All children in the study groups were representative by gender and age.

The clinical and laboratory investigation included a medical history, a physical examination, and a biochemical blood test to measure glucose, cholesterol, β-lipoproteins, total bilirubin, the thymol test, alanine amino-transferase (ALT) and aspartate amino-transferase (AST) levels. Additionally, the ALT/AST ratio, de Ritis index (AST/ALT), and Hepatic Steatosis Index (HSI = 8 · (ALT/AST) + BMI + 2, if female) were determined [18].

The presence of insulin resistance was determined using a homeostatic model by calculating the HOMA-IR index, using the following formula [24]:

HOMA-IR = fasting blood glucose level (mmol/l) × × fasting blood insulin level (μU/l) / 22.5.

The severity of IR was determined based on the insulin resistance index according to F. Caro [5]:

Caro index = glucose (mmol/l) / insulin (μU/l).

The criteria indicating IR were a HOMA-IR index exceeding 2.77 and a Caro index of less than 0.33 [22, 24].

Serum levels of insulin, leptin, adiponectin, osteopontin, resistin and aldosterone were measured using commercial enzyme-linked immunosorbent assay (ELISA) kits (Insulin ELISA (DRG, Germany), DRG Leptin ELISA EIA-2395 (Germany), Human Adiponectin ELISA (BioVendor, Germany), Osteopontin, ENZO LIFE SCIENCE AG (Switzerland), Human Resistin ELISA RD191016100 (BioVendor, Czech Republic) and Aldosterone (DRG, USA), respectively.

The study results were analysed using the licensed statistical software package Statistica for Windows 13.0 (number JPZ8041382130ARCN10-J) and SPSS 23.0 for Windows. Values of $p < 0.05$ were considered as significant for all types of analysis.

Permission was obtained from the Regional Bioethics Committee of Zaporizhzhia State Medical and Pharmaceutical University during the study planning. All procedures performed in studies involving children complied with the ethical standards of the Institutional and National Research Committee and the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. Informed consent was obtained from each of the participants included in the study and their legal guardians.

Results

A comparison of the anthropometric data of the children in the observation group showed that their body weight, BMI, waist circumference and hip circumference were higher than those of the control group, with the most pronounced values observed in the group of patients with obesity and MAFLD (Table 1).

Of particular note was the statistically significant increase in the waist-to-hip ratio and the waist-to-height ratio in patients with MAFLD compared with

Table 1
Anthropometric characteristics of study groups (M ± m)

Indicator	Obesity with MAFLD (n = 31)	Obesity without MAFLD (n = 33)	Control group (n = 34)
Age, years	13.87 ± 0.38	13.08 ± 0.44	14.09 ± 0.33
Body weight, kg	95.61 ± 3.21[1, 2]	81.42 ± 3.97[2]	52.85 ± 2.12
Height, cm	165.90 ± 1.80	164.36 ± 3.11	161.71 ± 2.35
BMI, kg/m^2	34.65 ± 0.98[1, 3]	29.83 ± 0.67[3]	19.91 ± 0.41
WC, cm	113.44 ± 3.29[1, 3]	97.85 ± 3.25[2]	63.92 ± 1.33
HC, cm	112.11 ± 2.47[1, 3]	104.00 ± 2.65[2]	82.92 ± 4.27
WHR, U	1.03 ± 0.03[1, 2]	0.93 ± 0.022	0.78 ± 0.02
WHtR, U	0.69 ± 0.01[1, 3]	0.63 ± 0.022	0.41 ± 0.01

Note. [1]$p < 0.05$ — compared with patients without fatty liver; [2]$p < 0.05$ — compared with the control group; [3]$p < 0.01$ — compared with the control group.

Table 2
Biochemical parameters of study groups (M ± m)

Indicator	Obesity with MAFLD (n = 31)	Obesity without MAFLD (n = 33)	Control group (n = 34)
Cholesterol, mmol/L	4.47 ± 0.23[2]	4.29 ± 0.19[2]	3.50 ± 0.28
β-lipoproteins, mmol/L	43.60 ± 2.81[2]	41.63 ± 2.69[2]	34.23 ± 2.11
Glucose, mmol/L	4.16 ± 0.12	4.12 ± 0.10	4.06 ± 0.1
AST, mmol/h/L	0.25 ± 0.03	0.18 ± 0.02	0.20 ± 0.02
ALT, mmol/h/L	0.48 ± 0.08[1, 2]	0.20 ± 0.03	0.26 ± 0.05
ALT/AST, U	1.91 ± 0.05[1, 2]	1.1 ± 0.02	1.25 ± 03
De Ritis coefficient, U	0.58 ± 0.07[1, 2]	0.94 ± 0.06	1.2 ± 0.03
Hepatic Steatosis Index, U	54.02 ± 2.41[1, 2]	39.96 ± 1.36[2]	29.54 ± 1.26
Caro index, U	0.20 ± 0.02[1, 2]	0.39 ± 0.03	0.44 ± 0.05
HOMA-IR index, U	4.45 ± 0.74[1, 3]	2.46 ± 0.20	2.04 ± 0.32

Note. [1]$p < 0.05$ — compared with patients without fatty liver; [2]$p < 0.05$ — compared with the control group; [3]$p < 0.01$ — compared with the control group.

obese children without MAFLD ($p < 0.05$), which indicated a predominance of abdominal adipose tissue and the development of abdominal obesity in this group.

It was noted that elevated serum levels of cholesterol, β-lipoproteins and the hepatosteatosis index ($p < 0.05$) in obese children occurred regardless of MAFLD presence. According to the comparisons, the development of MAFLD was accompanied by a statistically significant decrease in the de Ritis and Caro indices with a simultaneous increase in the ALT/AST ratio, the Hepatic Steatosis Index and the HOMA-IR index ($p < 0.05$) (Table 2).

Given that MAFLD is associated with impaired insulin function, and that hyperinsulinaemia triggers a vicious circle, namely leading to increased aldosterone levels, which, in turn, contributes to the development of insulin resistance by stimulating the maturation of adipocytes and increasing fat mass [8], we investigated the levels of these hormones in children with obesity. It was found that in the group of children with MAFLD, there was a statistically significant increase in serum insulin and aldosterone levels, whereas in obese patients without MAFLD, the levels of these hormones were within the range observed in the control group (Table 3).

Analysis of adipokine levels in children in the study groups revealed that the development of obesity was associated with statistically significantly higher serum level of osteopontin and lower serum level of adiponectin ($p < 0.05$). It should be noted that these changes were maximally pronounced in the group of children with obesity and MAFLD, significantly exceeding those obtained in both the control group ($p < 0.01$) and the group of children with obesity but without signs of MAFLD ($p < 0.05$). Serum levels of another specific secretory factor of adipose tissue (resistin) were also elevated in both groups of obese children compared with the control group ($p < 0.05$) and were not dependent on the presence of MAFLD.

We subsequently investigated serum leptin levels in the children we were monitoring. It was found that the highest leptin levels were in the group diagnosed with MAFLD. In the other group of patients, in whom obesity occurred without MAFLD, its concentration was significantly lower ($p < 0.05$) than in the presence of MAFLD, but statistically higher ($p < 0.05$) than in the control group.

To determine the relationship between body weight and leptin levels, we used the leptin-to-BMI ratio [44]. It was found that in the presence of MAFLD, the

Table 3
Serum levels of selected hormones in study groups (M ± m)

Indicator	Obesity with MAFLD (n = 31)	Obesity without MAFLD (n = 33)	Control group (n = 34)
Insulin, μIU/mL	22.84 ± 2.33[1, 3]	13.00 ± 1.45	12.43 ± 1.33
Aldosterone, pg/mL	540.77 ± 68.91[1, 3]	357.5 ± 25.30	315.56 ± 15.72
Adiponectin, μg/mL	1.63 ± 0.19[1, 3]	2.54 ± 0.38[2]	4.18 ± 0.57
Resistin, ng/mL	4.75 ± 0.62[2]	3.99 ± 0.44[2]	2.4 ± 0.27
Osteopontin, ng/mL	21.25 ± 2.67[1, 3]	13.53 ± 2.46[2]	7.62 ± 1.28
Leptin, ng/mL	43.72 ± 5.21[1, 3]	25.07 ± 3.83[2]	14.33 ± 1.33
Leptin/BMI, U	1.31 ± 0.16[1, 3]	0.78 ± 0.11	0.70 ± 0.07

Note. [1]$p < 0.05$ — compared with patients without fatty liver; [2]$p < 0.05$ — compared with the control group; [3]$p < 0.01$ — compared with the control group.

leptin-to-BMI ratio was higher, whereas in the comparison group, despite a moderate increase in serum leptin content, this ratio remained within the range observed in the control group ($p > 0.05$).

Serum leptin levels in obese children were directly correlated with insulin resistance, as evidenced by the inverse relationship with the Caro index ($r = –0.48$, $p < 0.05$) and a positive correlation with the HOMA-IR index ($r = +0.48$, $p < 0.05$). Elevated leptin levels were associated with the development of abdominal obesity, as evidenced by a significant correlation between serum leptin levels and the waist-to-hip ratio ($r = +0.43$, $p < 0.05$). Hyperleptinaemia in children with MAFLD, combined with obesity, may indicate a likely development of leptin resistance [23].

The presence of a moderate negative correlation between resistin and the Caro index ($r = –0.67$, $p < 0.01$), with no correlation with the HOMA-IR index, underscored its role in the development of insulin resistance [2, 11]. Conversely, the opposite pattern observed for adiponectin. Serum adiponectin demonstrated a negative correlation with the HOMA-IR index ($r = –0.35$, $p < 0.05$), with no association with the Caro index, confirming its protective role against insulin resistance [1].

A positive correlation was found between resistin and waist circumference ($r = +0.44$, $p < 0.05$) and hip circumference ($r = +0.58$, $p < 0.01$), as well as with cholesterol levels ($r = +0.54$, $p < 0.05$) and β-lipoproteins ($r = +0.63$, $p < 0.01$), and an inverse relationship between adiponectin and waist circumference ($r = –0.57$, $p < 0.05$) and hip circumference ($r = –0.55$, $p < 0.05$) and their ratio ($r = –0.53$, $p < 0.05$).

Based on the correlation analysis, a correlation matrix was constructed to illustrate the causal relationship between obesity with MAFLD and the studied indicators (Fig. 1).

Discussion

According to the results of the study, it was found that waist circumference, hip circumference, their ratio, and BMI were higher in patients with MAFLD than without this complication of obesity. Our findings indicate that clinicians should use these indicators in obese children when monitoring the course of MAFLD to ensure timely diagnosis of the disease's progression. This is because, as abdominal obesity develops, lipolysis in the portal vein leads to the formation of an excess of unsaturated free fatty acids. These free fatty acids are absorbed by the liver and undergo de novo lipogenesis, leading to the accumulation of triglycerides in hepatocytes, which, in turn, contributes to the development of hyperlipidaemia, insulin resistance and fatty liver disease [9, 20]. This is confirmed by our findings regarding a statistically significant decrease in the de Ritis and Caro ratios, accompanied by an increase in ALT, the ALT/AST ratio, the Hepatic Steatosis Index and the HOMA-IR index in children with obesity and MAFLD ($p < 0.05$). At the same time, AST levels remained within the range of the control group.

It has been proven that high ALT/AST ratio values indicate fatty liver disease and insulin resistance [12, 13, 26, 34]. A study by Y. Xuan et al., which analyzed the association between the ALT/AST ratio and MAFLD depending on the age of patients, showed that an elevated ALT/AST was associated with a higher risk of MAFLD in children and adolescents under the age of 20 compared with participants in other age groups. The authors therefore emphasise the need for clinicians to use the ALT/AST ratio in children and adolescents when monitoring the course and treatment of MAFLD, in order to improve the prognosis and prevent the progression of the disease [42].

It has been established that the development of MAFLD in obese children was accompanied by a statistically significant increase in serum insulin and aldosterone levels ($p < 0.05$). To date, the exact relationship between MAFLD with hyperinsulinaemia and insulin resistance remains unclear [7]. It is hypothesised that the development of MAFLD is accompanied by a reduction in hepatic insulin clearance, which ultimately leads to increased insulin secretion, a compensatory mechanism for systemic insulin resistance [19]. Previous studies have shown that hyperinsulinaemia can lead to a reduction in the downregulation of insulin receptors in hepatocytes, thereby reducing insulin clearance and further exacerbating hepatic

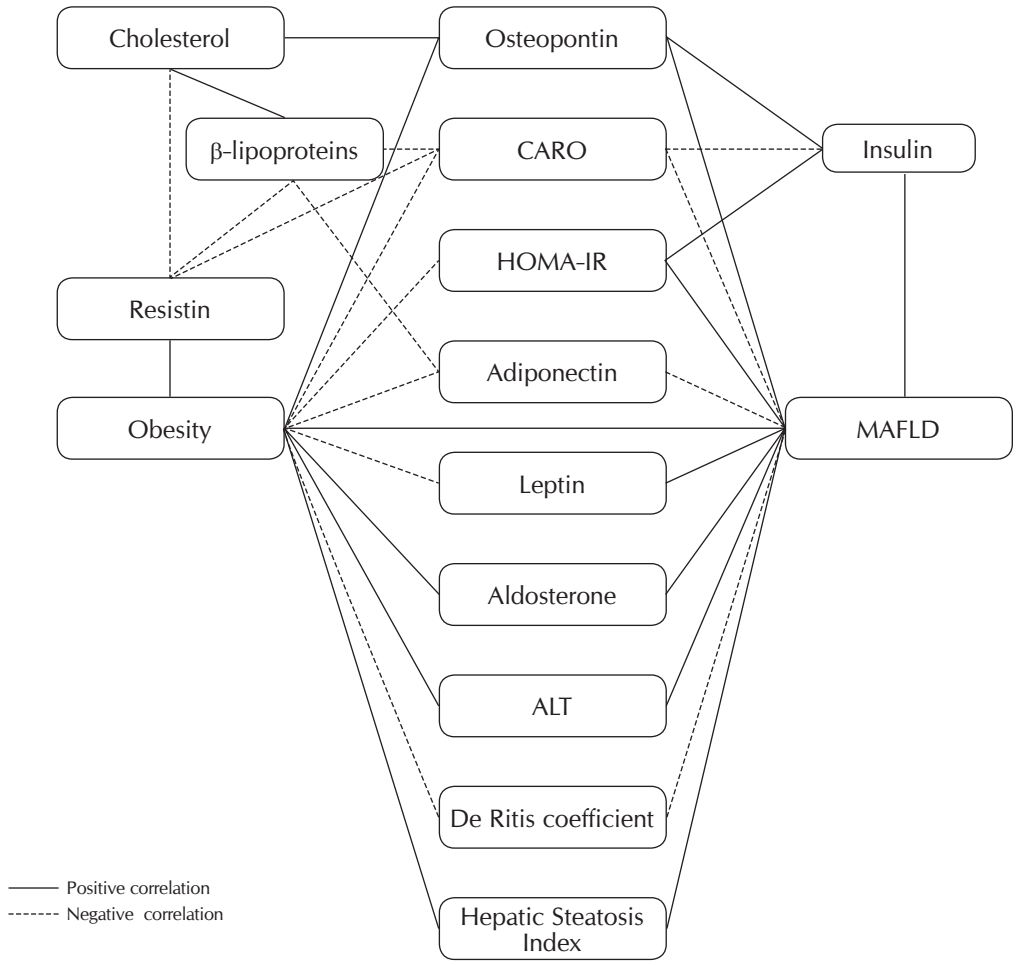

Fig. 1. **Correlations between biochemical parameters, hormone levels, adipokines, and obesity with MAFLD in children**

insulin resistance, creating a vicious circle [28]. A 10-year prospective study of non-diabetic individuals from the general population demonstrated that elevated aldosterone levels are independently associated with insulin resistance [27]. Furthermore, an excess of aldosterone exacerbates oxidative stress and inflammation and directly contributes to the activation of hepatic stellate cells and liver fibrosis [21].

To date, there are still unresolved questions regarding the relationship between liver metabolism and blood adipokine levels. However, given the obesity epidemic and the high incidence of fatty liver disease, analyzing the role of these compounds is of great importance for understanding the mechanisms of chronic liver damage, as well as for using them as markers of severity and planning treatment for metabolic-associated fatty liver disease [3].

Certain differences in adipokine synthesis have been identified in children with obesity and MAFLD. It has been demonstrated that the development of MAFLD against a background of obesity was accompanied by statistically higher serum levels of osteopontin and leptin, with a simultaneous reduction in serum adiponectin levels ($p < 0.05$). However, no statistically significant differences were found in resistin levels between groups of children with obesity, with or without MAFLD ($p > 0.05$).

Disruptions in adipokine production which affect various tissues, including the liver and adipose tissue itself are one of the causes of alterations in glucose homeostasis, insulin sensitivity, lipolysis and fatty acid oxidation [30]. This may contribute to other obesity-related complications, such as insulin resistance and MAFLD [6, 29]. It is believed that higher levels of leptin and resistin, along with lower levels of adiponectin, may serve as early biomarkers of obesity-related MAFLD and be used as an alternative to liver biopsy [10, 14, 43]. It has been shown that osteopontin promotes obesity and modulates lipid synthesis [35]. Experimental studies conducted on animal models of diet-induced obesity have found that neutralisation of osteopontin led to reduction in adipose tissue inflammation, improved insulin action in the liver and reduced hepatic triacylglycerol synthesis, thereby preventing the development of hepatic steatosis. Based on the obtained results, the authors concluded that this adipokine contributes to metabolic syndrome and fatty liver disease [15, 16].

The findings of the study formed the basis for constructing a diagram of the pathogenic mechanisms of

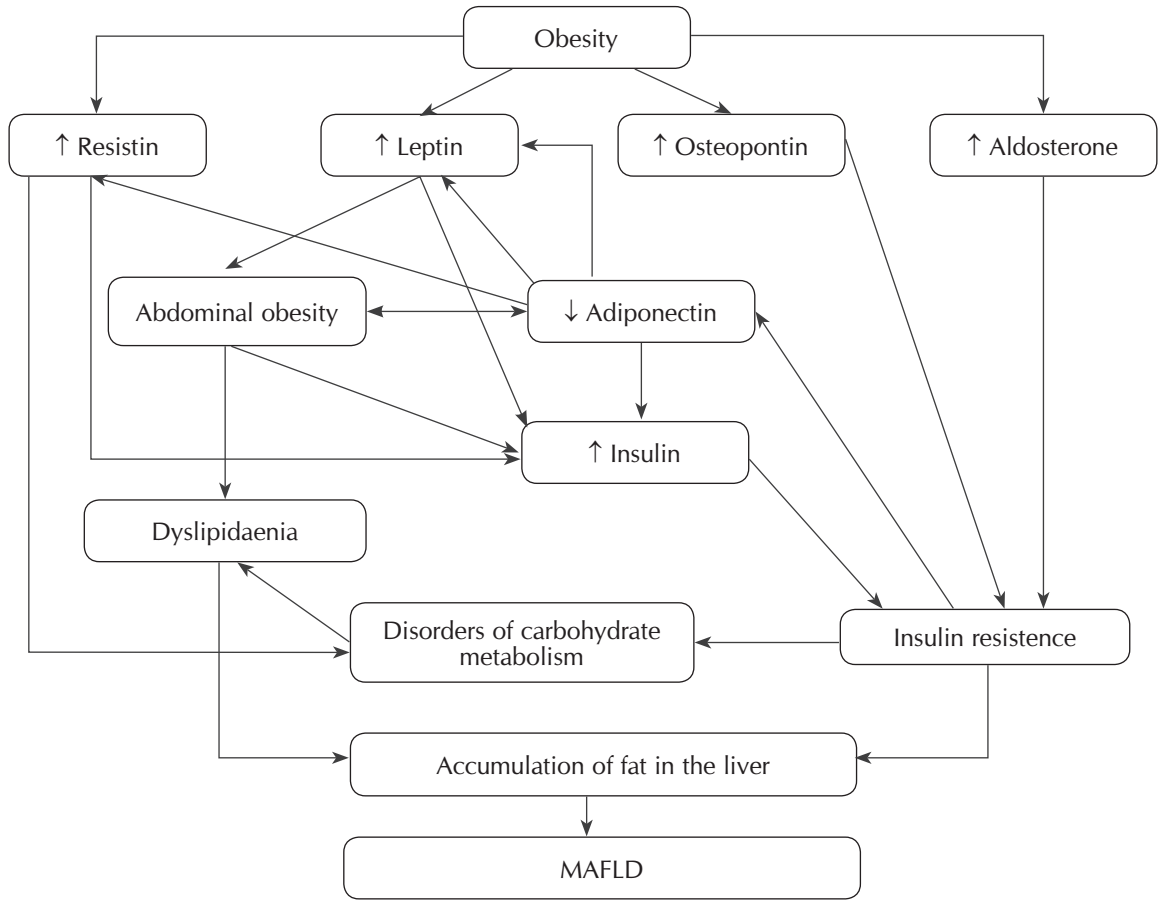

Fig. 2. **Pathogenic mechanisms of MAFLD development in children with obesity**

MAFLD development in obese children, which illustrates the hierarchical relationships between the studied parameters (Fig. 2).

Conclusions

1. The development of MAFLD in children with obesity is characterised by the formation of abdominal obesity, a decrease in the de Ritis ratio and the Caro index, accompanied by an increase in the Hepatic Steatosis Index and the HOMA-IR index.
2. Children with MAFLD have certain hormonal abnormalities, namely hyperaldosteronism and hyperinsulinism, combined with elevated serum osteopontin levels ($p < 0.05$).
3. In children with obesity accompanied by MAFLD, a number of characteristics regarding the supply of hormones synthesised by adipocytes were identified, namely: the highest leptin levels against a background of a maximal reduction in adiponectin levels, whilst resistin levels remained practically intact. A similar pattern was observed in the group of obese children without MAFLD, albeit at a significantly lower level ($p < 0.05$).
4. The development of MAFLD against a background of childhood obesity acts as a factor that exacerbates the course of the underlying disease, necessitating the implementation of measures aimed to prevent its occurrence and ensure timely treatment of complications.

The authors declare no conflict of interest.
Authors' participation: research concept and design, critical revision of the article, final approval of the article — H.O. Lezhenko; data analysis and interpretation, writing the article — O.Ye. Pashkova; collection and assembly of data, writing the article — K.V. Samoylyk.

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Метаболічно-асоційована жирова хвороба печінки у дітей з ожирінням. Погляд педіатра

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Мета роботи — дослідити особливості формування та перебігу метаболічно-асоційованої жирової хвороби печінки (МАЖХП) у дітей, хворих на ожиріння.

Матеріали та методи. Обстежено 64 хворих на ожиріння віком 11—17 років. В основну групу залучено 31 дитину з ожирінням, хвору на МАЖХП, у групу порівняння — 33 дитини з ожирінням без МАЖХП, у контрольну групу — 34 дитини, репрезентативних за віком і статтю без ожиріння та порушень вуглеводного обміну. Клініко-лабораторне обстеження передбачало збір анамнезу, фізикальне обстеження, біохімічний аналіз крові з визначенням рівня глюкози, холестерину, β-ліпопротеїнів, загального білірубіну, тимолової проби, рівня аланінамінотрансферази (АЛТ) й аспартатамінотрансферази (АСТ), АЛТ/АСТ, індекс де Рітіса (АСТ/АЛТ) і гепатостеатозного індексу. Наявність інсулінорезистентності та її виразність визначали за допомогою індексу HOMA-IR і коефіцієнта CARO відповідно. Дослідження вмісту інсуліну, лептину, адипонектину, остеопонтину, резистину й альдостерону в сироватці крові проводили з використанням комерційних наборів для імуноферментного аналізу. Результати дослідження опрацьовані із застосуванням статистичного ліцензійного пакета програм Statistica for Windows 13.0 та SPSS 23.0 for Windows.

Результати та обговорення. Установлено, що для дітей із МАЖХП притаманний абдомінальний тип ожиріння, що супроводжувалося зменшенням величини коефіцієнтів де Рітіса та CARO з одночасним збільшенням співвідношення АЛТ/АСТ, гепатостеатозного індексу та індексу HOMA-IR ($p < 0,05$). У групі дітей із МАЖХП зареєстровано вірогідне підвищення вмісту інсуліну й альдостерону в сироватці крові ($p < 0,05$), тоді як у пацієнтів з ожирінням без МАЖХП вміст зазначених гормонів не відрізнявся від контрольної групи. Розвиток ожиріння в дітей супроводжувався статистично вищим рівнем остеопонтину й лептину в сироватці крові та зниженням вмісту адипонектину з максимально виразними змінами в групі дітей із МАЖХП ($p < 0,01$). Рівень резистину в сироватці крові був підвищеним в обох групах дітей з ожирінням ($p < 0,05$) і не залежав від наявності МАЖХП. Визначені зміни адипокінів були найбільш значущими в пацієнтів з ознаками інсулінорезистентності. На підставі отриманих результатів побудовано схему патогенетичних механізмів розвитку МАЖХП у дітей, хворих на ожиріння.

Висновки. Розвиток МАЖХП на тлі ожиріння є чинником, що обтяжує перебіг основного захворювання і характеризується формуванням абдомінального ожиріння, гіперліпідемії, інсулінорезистентності та стеатозу печінки. Визначені зміни супроводжуються порушеннями гормонального статусу — гіперальдостеронізмом і гіперінсулінізмом, підвищенням вмісту в сироватці крові остеопонтину та лептину з одночасним зниженням рівня адипонектину ($p < 0,05$), концентрація резистину відповідала показникам, одержаним у дітей з ожирінням без МАЖХП. Отримані результати є підґрунтям для розробки заходів, спрямованих на профілактику виникнення МАЖХП у дітей з ожирінням та своєчасну терапію ускладнення.

Ключові слова: ожиріння, метаболічно-асоційована жирова хвороба печінки, інсулінорезистентність, адипокіни, діти.

ДЛЯ ЦИТУВАННЯ • *FOR CITATION*

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