ENDOCRINE STATUS OF ADOLESCENT GIRLS WITH NON-ALCOHOLIC FATTY LIVER DISEASE AND OBESITY

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Abstract

Along with the increase in the prevalence of childhood obesity, diseases associated with unhealthy morbid obesity, including non-alcoholic fatty liver disease (NAFLD), are also on the rise. How NAFLD affects the hormonal profile in adolescent girls has not been studied enough. Therefore, the aim of this study was to examine the features of the endocrine status of adolescent girls with NAFLD and obesity. Material and methods. From 2010 to 2020, 300 patients aged 12–17 years were monitored, including 120 patients with NAFLD and metabolically unhealthy obesity and 180 conditionally somatically healthy girls with normal sexual development with normal body weight. Clinical examination, biochemical assessment of the functional state of the liver and its morphostructure were performed. Determination of the level of peripheral blood serum hormones was performed by immunochromical method with chemiluminescent detection. Results. Endocrine status of girls with NAFLD and obesity was characterized by an increase in luteinizing hormone (LH) - 9.89 ± 0.18 vs. 5.13 ± 0.08 μIU / ml (p<0.01); follicle-stimulating hormone (FSH) - 5.50 ± 0.16 vs. 5.40 ± 0.07 μIU / ml (p<0.01); the ratio of LH / FSH - 1.91 ± 0.05 vs. 0.98 ± 0.02 (p<0.01); prolactin - 327.73 ± 7.15 vs. 282.93 ± 8.36 μIU / ml (p<0.01); thyroid-stimulating hormone (TSH) - 3.36 ± 0.07 vs. 2.15 ± 0.05 μIU / ml (p<0.01); decrease in estradiol level - 124.15 ± 2.39 vs. 437.45 ± 9.59 pmol / ml (p<0.01); progesterone - 1.49 ± 0.09 vs. 2.78 ± 0.08 nmol / ml (p<0.01); increase in the level of free testosterone - 1.96 ± 0.1 vs. 1.16 ± 0.04 nmol / l (p <0.01); free...
Conclusions. Endocrine status of girls with NAFLD and unhealthy morbid obesity during puberty is characterized by increased secretion of gonadotropins, prolactin and TSH, decreased levels of estradiol, progesterone, thyroid hormones against the background of a moderate increase of androgens, insulin and insulin resistance.

Key words: girls; puberty; obesity; nonalcoholic fatty liver disease; endocrine status.

Overweight has become a global pandemic. In many high-income countries, the number of overweight and obese children tends to increase [2]. A dangerous trend is that overweight is increasingly affecting low- and middle-income countries, where two-thirds of obese people currently live [11]. Among children and adolescents of Ukraine in the structure of diseases of the endocrine system obesity is 11.1%. Every year it is recorded in 1,820,000 children under the age of 17 [3]. Important risk factors for overweight and obesity are genetic predisposition, ethnicity, and individual behaviors such as low physical activity, increased free time spent on electronic screens, regular consumption of high-calorie foods, and socioeconomic status [16].

As the prevalence of childhood obesity increases, so do the diseases associated with unhealthy morbid obesity. Non-alcoholic fatty liver disease (NAFLD) is becoming one of the most common health problems in obese children and adolescents [5]. Hepatic steatosis is a clinical condition characterized by infiltration of fat in more than 5% of hepatocytes during liver biopsy, which is not associated with excessive alcohol consumption, autoimmune disease, viral infections or the use of steatogenic drugs [13]. NAFLD covers a range of histological changes in the liver from steatosis to nonalcoholic steatohepatitis, fibrosis, cirrhosis, end-stage liver disease and hepatocellular carcinoma [12].

The available data convincingly indicate that already in pediatric age the incidence of NAFLD extends beyond the liver and is associated with the main components of the metabolic syndrome [15, 24]. Metabolic syndrome is defined as the presence of three of the following five conditions: high serum triglycerides (TG), low serum high-density lipoproteins (HDL), hyperglycemia, central obesity and elevated systemic blood pressure. Metabolic syndrome is recognized as a strong risk factor for the development and progression of NAFLD [20].
In the pediatric population among obese children NAFLD is found in 40% of cases, while in adolescents with obesity complicated by metabolic syndrome, this figure reaches 70%, and in 13% of cases there are signs of non-alcoholic steatohepatitis [1].

Functional activity of the liver increases during puberty and reaches a maximum after puberty [27]. Sex hormones affect various physiological and biological functions, including the development and function of adipocytes [25, 26]. Insulin sensitivity decreases during puberty for unknown reasons [5]. Due to the fact that the liver makes a significant contribution to the metabolism of steroids [23], this undoubtedly has an impact on sexual development during puberty. How NAFLD and obesity affect the hormonal profile in adolescent girls has been insufficiently studied.

**The objective:** to examine the features of the endocrine status of adolescent girls with NAFLD and obesity.

**Material and methods.** From 2010 to 2020, 300 patients aged 12–17 years were monitored, of which 120 patients with NAFLD and with metabolically unhealthy obesity of the group NAFLD and 180 conditionally somatically healthy girls with normal sexual development and with normal body weight of group K.

A complete clinical examination, biochemical assessment of the functional state of the liver and its morphostructure using ultrasound and elastography of the hepatobiliary system according to standard methods. On a Cobas 6000 analyzer and using test systems from Roche Diagnostics GmbH (Switzerland) fasting serum glucose was studied by the hexokinase method; insulin – by immunochemical method with chemiluminescent detection; total cholesterol (cholesterol), HDL and low-density lipoprotein (LDL), γ-glutamate transferase (γ-GT) and TG – by enzymatic colorimetric method; alanine aminotransferase (ALT) and aspartate aminotransferase (AST) – by kinetic method. The content of C-peptide was determined by immunochemical method with chemiluminescent detection using an analyzer and Immunilite test system (Siemens AG, Germany); uric acid – by colorimetric method; adiponectin – by enzyme-linked immunosorbent assay (ELISA) using an analyzer and test system Mediagnost GmbH (Germany); leptin - by ELISA using an analyzer and LDN test system (Germany). Insulin resistance index HOMA-IR (Homeostasis Model Assessment of Insulin Resistance – assessment of homeostasis model for insulin resistance) was calculated by the formula HOMA-IR = fasting insulin (μU / fasting serum glucose (mmol / l) / 22.5.

Obesity was assessed according to WHO standards, with an estimate of the SDS standard deviation if the BMI / age ratio exceeded the median value specified in the Standard Physical Development Indicators of Children (WHO) by more than two standard deviations.
Determination of peripheral blood serum hormones was performed by immunochemical method with chemiluminescent detection using Roche Diagnostics kits (Switzerland) on a Cobas 6000 analyzer (e 601 module): luteinizing hormone (LH), follicle-stimulating hormone (FSH), prolactin (PRL), thyroid-stimulating hormone (TSH), free triiodothyronine (fT3), free thyroxine (fT4), estradiol (E2), free testosterone (fT).

The obtained data were processed statistically using the Excel software package 10. Calculated the mean value (M), standard deviation error (SE). Student's t-test, Wilcoxon-Mann-Whitney U-test, Fisher's φ-test, and χ² were used to identify differences between the comparative indicators. Correlations and associations of traits were calculated using Spearman's criterion for abnormal trait distribution and Pearson's criterion for normal trait distribution.

Results and its discussion. In obese girls, NAFLD was manifested by elevated levels of hepatic transferases; changes in carbohydrate metabolism with a probable increase in levels of glucose and insulin, C-peptide, the formation of insulin resistance; disorders of lipid metabolism with increased production of leptin, total cholesterol, LDL, TG and decreased levels of adiponectin and HDL; disorders of purine metabolism with increased uric acid (Table 1).

| Indicator                  | Group                  |
|----------------------------|------------------------|
| ALT, U/l                   | NAFLD, n=120           |
|                            | 32.02±0.70 k           |
|                            | K, n=180               |
|                            | 14.77±0.28             |
| AST, U/l                   | 22.39±0.51 k           |
| γ-GT, U/l                  | 20.07±0.44 k           |
| Glucose, mmol/l            | 5.64±0.05 k            |
| Insulin, μU / ml           | 16.79±0.68 k           |
| HOMA-IR                    | 4.32±0.20 k            |
| C-peptide, ng / ml         | 4.16±0.21 k            |
| Total cholesterol, mmol / l| 5.57±0.07 k            |
| HDL, mmol / l              | 1.11±0.01 k            |
| LDL, mmol / l              | 2.78±0.04 k            |
| TG, mg / dl                | 1.65±0.02 k            |
| Uric acid, μmol/l          | 361.07±4.46 k          |
| Leptin, ng / ml            | 64.15±1.84 k           |
| Adiponectin, μg / ml       | 6.00±0.17 k            |

Note. k – statistically significant reliability with a similar indicator of group K (p<0.05).

The main regulators of ovarian activity are FSH, LH and PRL. The secretion of FSH and LH is under double control: by hypothalamic gonadotropin-releasing factor and sex
steroids. Ovulation requires not only the proper basal level of hormone secretion and their ratio, but also the presence of the correct cyclic emissions. The profile of pituitary hormones in girls with NAFLD and obesity was characterized by elevated average levels of LH (9.89 ± 0.18 vs. 4.46 ± 0.10 μIU / ml, p<0.01), FSH (5.50 ± 0.16 vs. 5, 40 ± 0.07 μIU / ml, p<0.01), the ratio of LH / FSH (1.91 ± 0.05 vs. 0.85 ± 0.02, p<0.01), PRL (327.73 ± 7.15 vs. 282.93 ± 8.36 μIU / ml, p<0.01). A similar trend was observed in all age groups (Table 2).

| Age, years | Group | LH, μIU / ml | FSH, μIU / ml | LH / FSH | PRL, μIU / ml |
|------------|-------|--------------|---------------|----------|--------------|
| 12         | NAFLD | 8.59±0.43 k  | 3.59±0.08 k   | 2.45±0.18 k | 328.26±6.01 k |
| K          | 3.53±0.10 | 5.40±0.18 | 0.67±0.03 | 242.39±25.83 |
| 13         | NAFLD | 8.75±0.30 k  | 3.92±0.17 k   | 2.28±0.09 k | 294.03±12.38 k |
| K          | 3.79±0.15 | 5.18±0.12 | 0.74±0.03 | 258.89±11.82 |
| 14         | NAFLD | 9.38±0.51 k  | 4.88±0.26 k   | 1.92±0.01 k | 308.36±9.18 k |
| K          | 3.91±0.15 | 5.21±0.13 | 0.77±0.04 | 256.20±11.82 |
| 15         | NAFLD | 9.92±0.30 k  | 6.11±0.20 k   | 1.64±0.06 k | 322.19±21.86 k |
| K          | 4.08±0.15 | 5.43±0.19 | 1.11±0.04 | 302.00±18.85 |
| 16         | NAFLD | 11.24±0.42 k | 7.08±0.24 k   | 1.60±0.06 k | 347.33±27.07 k |
| K          | 5.48±0.26 | 5.67±0.14 | 0.99±0.06 | 316.76±26.94 |
| 17         | NAFLD | 11.45±0.33 k | 7.39±0.21 k   | 1.55±0.01 k | 366.23±18.72 k |
| K          | 5.98±0.25 | 5.43±0.19 | 1.11±0.04 | 321.34±9.29 |

Note. k – statistically significant reliability with a similar indicator of group K (p<0.05).

As can be seen from table 2, with age, the levels of gonadotropins and PRL in the group NAFLD increased, while the ratio of LH / FSH decreased from 2.45 ± 0.18 in the age group of 12 years to 1.55 ± 0.01 in the age group of 17 years.

The study of sex hormone levels revealed a decrease in the levels of sex steroids, such as E₂ and P₄ in both the general group and in all age categories in NAFLD (Table 3).

Thus, the average total level of E₂ in the group NAFLD was 124.15 ± 2.39 vs. 437.45 ± 9.59 pmol / ml in the group K (p<0.01), P₄ – 1.49 ± 0.09 vs. 2.78 ± 0.08 nmol / ml (p<0.01). At the same time, in girls with NAFLD, insulin-resistant hyperinsulinism contributes to obesity and excessive androgen synthesis. Thus, in the NAFLD group there was a moderate increase in the level of fT compared to a similar indicator in all age groups. The mean total fT level in patients with NAFLD was 1.96 ± 0.10 nmol / l vs. 1.16 ± 0.04 nmol / l in the control group (p<0.01).
Table 3

Levels of sex hormones in the examined girls of pubertal age, M ± SE

| Age, years | Group | E₂, pmol / l | P₄, nmol / l | fT, nmol / l |
|------------|-------|--------------|-------------|-------------|
| 12         | NAFLD | 112.60±1.52  | 0.98±0.09   | 1.50±0.13   |
|            | K     | 288.83±12.30 | 1.71±0.14   | 0.92±0.07   |
| 13         | NAFLD | 119.30±2.79  | 1.11±0.13   | 1.86±0.20   |
|            | K     | 295.83±7.92  | 2.28±0.16   | 0.99±0.07   |
| 14         | NAFLD | 119.30±2.79  | 1.11±0.13   | 1.86±0.20   |
|            | K     | 434.78±9.31  | 2.82±0.19   | 1.02±0.07   |
| 15         | NAFLD | 121.06±1.95  | 1.38±0.10   | 1.89±0.15   |
|            | K     | 463.89±10.62 | 2.87±0.16   | 1.16±0.07   |
| 16         | NAFLD | 130.37±2.71  | 1.63±0.08   | 2.17±0.23   |
|            | K     | 539.92±11.52 | 2.90±0.14   | 1.32±0.11   |
| 17         | NAFLD | 126.32±4.62  | 2.64±0.10   | 2.10±0.13   |
|            | K     | 601.46±9.47  | 4.08±0.08   | 1.54±0.10   |

Note.  k – statistically significant reliability with a similar indicator of group K (p<0.05).

Of course, a moderate increase in androgens stimulates LH production both at the level of the hypothalamus and at the level of the pituitary gland, while their high levels suppress LH [25]. Insulin acts synergistically with gonadotropins, regulating the formation of androgens, i.e. the ovaries function as sensitive to the action of insulin on steroidogenesis in a state of peripheral resistance to the action of insulin on glucose metabolism. Lipogenesis of adipocytes, similar to ovarian steroidogenesis, is also sensitive to insulin. One of the actions of insulin is to stimulate testosterone production with 17β-HSD5. Thus, hyperinsulinemia in NAFLD, which compensates for insulin resistance, contributes to an excess of both androgens and fat mass [21]. In turn, hyperandrogenic ovarian dysfunction and insulin resistance contribute to increased PRL levels [17]. According to the literature, elevated PRL levels are common in patients with liver cirrhosis and in 40% of patients with hypothyroidism [22].

A significant direct correlation between the content of LH in the serum (r = 0.29, p<0.02), fT (r = 0.33, p<0.01) and the inverse – the level of E₂ (r = -0.57, p<0.04) with the level of PRL. This suggests that the development of ovarian dysfunction in conditions of hyperandrogenism and elevated PRL levels may be due to changes in ovarian sensitivity to gonadotrophic stimulation (decreased sensitivity to FSH and increased sensitivity to LH). The combination of these processes leads to inhibition of the synthesis of E₂, P₄, disorders of ovarian steroidogenesis and folliculogenesis.
The level of TSH in patients with NAFLD was higher than in the control – 3.36 ± 0.07 vs. 2.15 ± 0.05 μIU / ml (p<0.01). The content of fT3 and fT4 in the group with NAFLD was equal to 4.41 ± 0.12 pmol / l and 14.61 ± 0.41 pmol / l was less than that in the control (5.46 ± 0.07 pmol / l (p<0.01) and 18.55 ± 0.20 pmol / l (p <0.01)). Similar trends in the levels of TSH and thyroid hormones were observed in all study age groups (Table 4).

**Table 4**

Levels of TSH and thyroid hormones in the examined girls of pubertal age, M ± SE

| Age, years | Group | TSH, μMO / ml | fT3, pmol / l | fT4, pmol / l |
|-----------|-------|---------------|--------------|--------------|
| 12        | NAFLD | 3.41±0.13     | 3.84±0.19    | 12.71±0.64   |
|           | K     | 2.22±0.14     | 4.88±0.16    | 19.63±0.35   |
| 13        | NAFLD | 3.26±0.21     | 3.73±0.17    | 12.34±0.58   |
|           | K     | 2.19±0.11     | 5.21±0.18    | 18.82±0.49   |
| 14        | NAFLD | 3.26±0.21     | 3.73±0.17    | 12.34±0.58   |
|           | K     | 2.37±0.13     | 5.39±0.13    | 19.22±0.35   |
| 15        | NAFLD | 3.18±0.14     | 4.58±0.22    | 15.17±0.73   |
|           | K     | 2.20±0.13     | 5.47±0.18    | 18.11±0.53   |
| 16        | NAFLD | 3.46±0.23     | 5.12±0.43    | 16.95±1.43   |
|           | K     | 1.96±0.16     | 5.68±0.18    | 18.30±0.55   |
| 17        | NAFLD | 3.58±0.06     | 5.48±0.32    | 18.14±1.07   |
|           | K     | 1.93±0.13     | 6.16±0.18    | 17.23±0.56   |

Note. k – statistically significant reliability with a similar indicator of group K (p<0.05).

The development of chronic inflammation in the liver parenchyma is closely associated with the phenomenon of "lipotoxicity". The increase in the concentration of free fatty acids in the serum due to persistent lipolysis, a lipid peroxidation reaction, is considered one of the reasons for the transformation of fatty infiltration of the liver (steatosis) into non-alcoholic steatohepatitis [2]. In response to lipid-induced hepatocellular damage, inflammatory masses are activated, endoplasmic reticulum and oxidative stress increase, leading to the production of proinflammatory cytokines, lipid peroxidation, hepatocyte cell death (increased apoptosis, and apoptosis). Chronic hepatocyte damage causes recruitment and activation of the Toll-like receptor of inflammatory cells, mainly liver macrophages or Kupffer cells, which enhances inflammation and apoptosis. Kupffer cells also produce activating factors (platelet-derived growth factor and transforming growth factor-β) to activate stellar liver cells that proliferate and secrete collagen, as well as other extracellular matrix proteins, leading to fibrosis [4].
Exposure to hepatocytes of high levels of lipids and carbohydrates contributes to lipotoxicity and glucotoxicity, which, in turn, leads to mitochondrial defects, endoplasmic reticulum stress and oxidative stress [7, 18]. Ectopic accumulation of toxic lipid intermediates triggers inflammatory pathway activation, cellular dysfunction and lipoapoptosis, these features contribute to the progression of NAFLD and liver damage [8, 9, 24]. Obesity also affects the liver due to unbalanced secretion of adipokines, having different effects on insulin resistance, hepatic steatosis, inflammation and fibrosis [19]. For example, obesity-related decreases in adiponectin levels contribute to insulin resistance and hepatic steatosis, while elevated leptin levels cause liver inflammation [19].

One of the reasons for the development of NAFLD is insulin resistance [10, 14], which we observed in the examined girls with this pathology (HOMA-IR 4.32 ± 0.20 vs. 2.27 ± 0.03, p<0.01). Various mediators (tumor necrosis factor-α (TNF-α), transforming growth factor-β, interleukin-6, etc.) are actively secreted and regulated in adipose tissue by insulin sensitivity. In particular, TNF-α activates the kappa-kinase-β inhibitor in adipocytes and hepatocytes, which leads to impaired binding of insulin to the receptor. The effect of TNF-α on the insulin receptor type I is manifested in its phosphorylation, which reduces its tropism to insulin, reduces the amount of transport protein GLUT-4, which carries glucose into the cell. There is evidence that the decrease in mitochondrial β-oxidation in the liver is associated with a slowdown in the production of transcription factor receptors activated by peroxisome proliferator-α (PPAR-α) in adipose tissue, which is determined in obesity, while in healthy people the transcription factor PPAR-α is activated by binding to long-chain fatty acids and increases the formation of oxidative cleavage enzymes of fatty acids and mitochondrial transport protein [28].

Hepatocytes are the most common type of cells in the liver (they make up 80% of the liver mass). Estrogens in hepatocytes act mainly through estrogen receptors-α ERα, limit gluconeogenesis, prevent increased hepatic glucose production and insulin resistance, limit the absorption of free fatty acids, inhibit de novo lipogenesis (synthesis of free fatty acids in the liver) and promote thereby preventing the deposition of lipids in the liver and the generation of lipotoxicity and reactive oxygen species, which cause a pro-inflammatory reaction, act as a driver of NAFLD progression and liver degeneration [6]. Based on the literature, it can be assumed that lower estrogen levels in girls with NAFLD contribute to the persistence and progression of inflammation in the liver due to increased production of proinflammatory cytokines, apoptosis and regeneration of liver cells, thereby causing further
liver damage [6]. In turn, the violation of the morphofunctional properties of the liver changes, as studies have shown, the endocrine status of girls at puberty.

**Conclusions**

Endocrine status of girls with NAFLD and unhealthy morbid obesity during puberty is characterized by increased secretion of gonadotropins, prolactin and TSH, decreased levels of E2, P4, thyroid hormones against the background of a moderate increase of androgens, insulin and insulin resistance.

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