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METABOLIC FATTY LIVER DISEASE AS A RISK FACTOR FOR EARLY RENAL DYSFUNCTION IN WOMEN OF REPRODUCTIVE AGE

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МЕТАБОЛИЧЕСКИ АССОЦИИРОВАННАЯ ЖИРОВАЯ БОЛЕЗНЬ ПЕЧЕНИ КАК ФАКТОР РИСКА РАННЕЙ РЕНАЛЬНОЙ ДИСФУНКЦИИ У ЖЕНЩИН РЕПРОДУКТИВНОГО ВОЗРАСТА

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Objective. To study the correlation of adipocytokines with early renal dysfunction indicators in women of reproductive age with obesity and metabolic fatty liver disease.
Materials and methods. The study included 100 obese females divided into 2 groups. The 1st group consisted of patients ($n = 50$) diagnosed with metabolic fatty liver disease aged 40.5 ± 2.8, and the 2nd group contained patients ($n = 50$) without metabolic fatty liver disease (MFLD). The level of insulin, cystatin C, resistin, leptin, monocyte chemoattractant protein (MCP-1), vascular endothelial growth factor (VEGF), interleukin 6 (IL-6), tumor necrosis factor α (TNF) were determined in blood serum by enzyme-linked immunosorbent assay (ELISA) method. Albumin-to-creatinine ratio, TNF- α, MCP-1, IL 6, cystatin C, β_2-microglobulin, VEGF were determined in morning urine.
Results. Increased levels of pro-inflammatory cytokines and endothelial dysfunction were revealed in group 1 in relation to both the comparison and control groups. In patients with MFLD associations of resistin level were the following: with HOMA($r = 0.60$), alanine aminotransferase (ALT) ($r = 0.54$), aspartate aminotransferase ($r = 0.71$), gamma-glutamyl transpeptidase ($r = 0.71$), high-density lipoprotein (HDL) ($r = -0.54$), VEGF ($r = 0.54$), TNF-α ($r = 0.44$), MCP-1 ($r = 0.57$) $p<0.05$. In the 1st and 2nd groups cytokine urinary excretion and renal dysfunction markers were higher than in the control group. Associations of urinary excretion of β_2-microglobulin with BMI ($r = 0.33$), HOMA ($r = 0.34$), resistin ($r = 0.30$), uric acid level ($r = 0.50$),

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creatinine ($r = 0.34$), thyroglobulin ($r = 0.31$), urinary MCP-1($r = 0.60$), IL-6 ($r = 0.70$) $p<0.05$ were revealed in the 1st group. In group 1 associations of urinary IL 6 with BMI ($r = 0.35$), waist/hip circumference (WC/HC) ($r = 0.33$), uric acid level ($r = 0.44$), urinary MCP-1($r = 0.74$) were positive, and associations with HDL ($r = -0.44$) $p<0.05$.
Conclusions. Resistin can be considered as an unfavourable marker of cardiometabolic disturbances in patients with MFLD. The association of subclinical inflammation markers and endothelial dysfunction with the markers of early renal impairment in patients with MFLD which was determined allows to expand the understanding of cardio-renal-metabolic continuum.
Keywords. Metabolic non-alcoholic fatty liver disease, early renal dysfunction, adipocytokines, obesity.

Цель. У женщин репродуктивного возраста с ожирением и МАЖБП изучена взаимосвязь адипоцитокинов с показателями ранней ренальной дисфункции.
Материалы и методы. В исследование были включены 100 женщин с ожирением, которых распределили по группам: 1-я группа – пациенты ($n = 50$) с установленной МАЖБП, возраст 40,5 ± 2,8 г., 2-я группа – пациенты ($n = 50$) без МАЖБП. В сыворотке крови методом ИФА определяли: уровень инсулина, цистатина С, резистина, лептина, моноцитарный хематтрактантный протеин (MCP-1), васкулоэндотелиальный фактор роста (ВЭФР), интерлейкин 6 (IL-6), фактор некроза опухоли альфа (ФНО-α). В утренней порции мочи определяли соотношение «альбумин/креатинин», ФНО-α, MCP-1, IL-6, цистатин С, β_2-микроглобулин, ВЭФР.
Результаты. В 1-й группе выявлены повышенные уровня провоспалительных цитокинов и дисфункции эндотелия относительно как данных группы сравнения, так и группы контроля. В группе с МАЖБП получены ассоциации уровня резистина с HOMA ($r = 0,60$), АЛТ ($r = 0,54$), АСТ ($r = 0,71$), ГГТП ($r = 0,71$), ЛПВП ($r = -0,54$), ВЭФР ($r = 0,54$), ФНО-α ($r = 0,44$) и MCP-1 ($r = 0,57$) $p < 0,05$. В 1-й и 2-й группах мочевая экскреция цитокинов и маркеров ренальной дисфункции превышала значения группы контроля. В 1-й группе выявлены связи мочевой экскреции β_2-микроглобулина с ИМТ ($r = 0,33$), HOMA ($r = 0,34$), резистина ($r = 0,30$), уровнем мочевой кислоты ($r = 0,50$), креатинина ($r = 0,34$), ТГ ($r = 0,31$), мочевыми MCP-1 ($r = 0,60$) и IL-6 ($r = 0,70$), $p < 0,05$. В 1-й группе IL-6 мочи имел положительные связи с ИМТ ($r = 0,35$), ОТ/ОБ ($r = 0,33$), уровнем мочевой кислоты ($r = 0,44$), мочевым MCP 1 ($r = 0,74$) и отрицательную с ХС ЛПВП ($r = -0,44$) $p < 0,05$.
Выводы. Резистин может быть рассмотрен в качестве неблагоприятного маркера кардиометаболических нарушений у лиц с МАЖБП. Установленная взаимосвязь маркеров субклинического воспаления и дисфункции эндотелия с маркерами раннего почечного повреждения у больных с МАЖБП позволяет расширить представления о кардио-рено-метаболическом континууме.
Ключевые слова. Метаболически ассоциированная неалкогольная жировая болезнь печени, ранняя ренальная дисфункция, адипоцитокины, ожирение.

INTRODUCTION

There are 33 million obese people in the Russian Federation*. It has been proven that metabolic syndrome in combination with non-alcoholic fatty liver disease (NAFLD) is associated with an increased risk of cardiovascular death, in this regard, in 2020, the European Society of Gastroenterologists proposed to combine the combination of metabolic syndrome with fatty liver disease into the concept of metabolically associated fatty liver disease (MAFLD) [1; 2]. The number of patients with chronic kidney disease (CKD) is increasing annually in the world, as of 2019, the disease was detected in 850 million people [3]. The significant contribution of fatty disease to the development and progression of CKD is beyond doubt. The prevalence of CKD in patients with fatty liver disease is 20–50 % [4; 5]. The mechanism of renal dysfunction in patients with MAFLD has not been fully studied. The liver is a generator of markers of inflammation, endothelial dys-

function and fibrosis, which can serve as binding components in the development of renal dysfunction in patients with MAFLD [6]. In turn, adipose tissue secretes a number of hormones that can have a simultaneous damaging effect on hepatocytes and nephron, triggering a cascade of cardio-hepato-reno-metabolic disorders [7]. The study of the involvement of MAFLD in the development of renal dysfunction in women of reproductive age is of clinical interest.

The objective of the study was to investigate the relationship of adipocytokines with indicators of early renal dysfunction in women of reproductive age with obesity and MAFLD.

MATERIALS AND METHODS

Groups under supervision:

Group 1 consisted of 50 women with obesity and MAFLD having no signs of alcoholic liver damage, suffering from hypertension, diabetes mellitus, functional and organic kidney damage. The average age of the patients was 40.5 ± 2.8 years and body mass index (BMI) = 35.6 ± 3.4 kg/m^2.

Group 2: 50 women without MAFLD. The average age was 39.6 ± 1.8 years and BMI = 34.7 ± 3.2 kg/m^2.

Control group: 30 healthy women, whose average age was 39.6 ± 4.3 years, BMI = 21.7 ± 1.8 kg/m^2.

The diagnosis of MAFLD was established in accordance with clinical recommendations EASL–EASD–EASO for the diagnosis and treatment of this disease [2]. Liver steatosis was determined by ultrasound diagnostics. Liver fibrosis was assessed using fibroelastography. Serum levels of cystatin C, insulin, leptin, resistin, monocyte chemattractant protein (MCP-1), interleukin 6 (IL-6), vascular endothelial growth factor (VEGF), tumor necrosis factor alpha (TNF-α) were determined by ELISA (enzyme-linked immunosorbent assay). TNF-α, MCP-1, albumin-to-creatinine ratio, IL-6, β_2-microglobulin, cystatin C, and VEGF were tested in the morning urine portion. The glomerular filtration rate (GFR) was calculated using the CKD-EPI equation. The following biochemical parameters were studied in blood serum: aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyltranspeptidase (γ-GTP), glucose, total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), tyriglycerides (TG), creatinine. The Fatty Liver Index (FLI) included an assessment of the level of TG and γ-GTP, body mass index (BMI) and waist circumference (WC). Follicle-stimulating hormone (FSH) was evaluated using immunochemiluminescence analysis (IHLA). The statistical processing of the obtained data was carried out with Statistica 12.0 software. The 3 groups were compared using the Kruskal – Wallis test, a pairwise comparison of groups with a normal distribution was performed using the Bonferroni–corrected *t*-test, in groups with an abnormal distribution the Mann – Whitney *U*-test was used. A statistically significant dependence was calculated at $p < 0.05$.

RESULTS AND DISCUSSION

The metabolic profile in the groups is presented in the table.

It is noteworthy that, despite abdominal obesity and proven liver steatosis, markers of metabolic syndrome were not fully represented in Group 1 patients. Naturally, an increase in the HOMA index, TG and uric acid levels was obtained, while the level of glucose and LDL and HDL cholesterol did not differ in Group 1 and Group 2 patients. Despite the increased level of cystatin C in Group 1, there were no significant differences in the calculated GFR between the groups. Group 2 patients demonstrated an increase in blood glucose, uric acid, and γ-GTP levels, while the parameters remained in the reference range. In Group 2, ALT was associated with HOMA ($r = 0.36$), γ-GTP ($r = 0.42$), LDL cholesterol ($r = 0.39$) $p < 0.05$. In the group without MAFLD, FLI was correlated with the levels of HOMA, glucose ($r = 0.4$ and $r = 0.3$, $p < 0.05$) and resistin ($r = 0.1$, $p < 0.05$).

During the study, adipocytokine activity was analyzed in comparison groups. As expected, levels of cytokines were significantly higher in the group with obesity and MAFLD relative to the data of the comparison group: resistin – (4.0 [2.5; 4.9] vs. 3.1 [2.7; 4.3] ng/ml, $p = 0.04$), leptin – (23.6 [17.2; 31.8] vs. 18.5 [11.8; 19.9] ng/ml, $p = 0.04$), TNF-α – (1.7 [1; 2.1] vs. 0.9 [0.6; 1.6] pg/ml, $p = 0.04$), VEGF – (293.7 [120.5; 435.2] vs. 155.9 [80.9; 255.6] pg/ml, $p = 0.04$), MCP-1 – (207.6 [148.7; 265.9] vs. 163.2 [125.8; 230.8] pg/ml, $p = 0.04$), IL-6 (1.8 [1.2; 2.2] vs. 1.10 [1; 1.3] pg/ml, $p = 0.03$).

Metabolic parameters in the groups ($M \pm 2m$); Kruskal – Wallis test H (2, $N = 130$)

Parameter	Group 1 $n = 50$	Group 2 $n = 50$	Control, $n = 30$	p
SBP, mmHg	128.2 ± 10.0	111.9 ± 7.0	113.3 ± 9.0	$p = 0.40$ $p_{1-2} = 0.04$ $p_{1-c} = 0.04$ $p_{2-c} = 0.40$
DBP, mmHg	84.1 ± 5	75.8 ± 4.2	79.8 ± 4.2	$p = 0.33$ $p_{1-2} = 0.04$ $p_{1-c} = 0.05$ $p_{2-c} = 0.10$
WC/HC	1.0 ± 0.1	0.8 ± 0.3	0.8 ± 0.2	$p = 0.65$ $p_{1-2} = 0.04$ $p_{1-c} = 0.04$ $p_{2-c} = 0.90$
TC, mmol/l	5.3 ± 0.6	5.05 ± 0.8	5.04 ± 0.8	$p = 0.80$ $p_{1-2} = 0.60$ $p_{1-c} = 0.10$ $p_{2-c} = 0.90$

Continuation of the table

Parameter	Group 1 *n*= 50	Group 2 *n*= 50	Control, *n*= 30	*p*
LDL-C, mmol/l	3.6 ± 0.6	3.0 ± 0.7	2.5 ± 0.5	$p = 0.22$ $p_{1-2} = 0.1$ $p_{1-c} = 0.04$ $p_{2-c} = 0.06$
HDL-C, mmol/l	1.3 ± 0.1	1.5 ± 0.2	1.5 ± 0.1	$p = 0.51$ $p_{1-2} = 0.05$ $p_{1-c} = 0.05$ $p_{2-c} = 0.90$
TG, mmol/l	2.7 ± 0.7	1.0 ± 0.3	1.0 ± 0.1	$p = 0.04$ $p_{1-2} = 0.02$ $p_{1-c} = 0.02$ $p_{2-c} = 0.10$
ALT U/l	45.3 ± 10.3	14.4 ± 6.8	14.3 ± 7.3	$p = 0.01$ $p_{1-2} = 0.001$ $p_{1-c} = 0.001$ $p_{2-c} = 0.1$
AST U/l	30.7 ± 16.2	17.5 ± 8.2	17.9 ± 9.5	$p = 0.04$ $p_{1-2} = 0.01$ $p_{1-c} = 0.01$ $p_{2-c} = 0.10$
Glucose, mmol/l	5.2 ± 0.6	4.9 ± 0.4	4.5 ± 0.2	$p = 0.10$ $p_{1-2} = 0.06$ $p_{1-c} = 0.04$ $p_{2-c} = 0.04$
Uric acid, μmol/l	306 ± 45.8	256 ± 58.3	220.2 ± 35.7	$p = 0.05$ $p_{1-2} = 0.04$ $p_{1-c} = 0.02$ $p_{2-c} = 0.04$
γ-GTP, U/l	48.7 ± 15.6	23.7 ± 13.5	16.7 ± 5.8	$p = 0.03$ $p_{1-2} = 0.01$ $p_{1-c} = 0.001$ $p_{2-c} = 0.04$
Cystatin C, ng/ml	0.90 ± 0.1	0.85 ± 0.1	0.83 ± 0.1	$p = 0.05$ $p_{1-2} = 0.04$ $p_{1-c} = 0.03$ $p_{2-c} = 0.07$
Creatinine, μmol/l	76.2 ± 4.9	74.0 ± 6.9	75.1 ± 7.0	$p = 0.60$ $p_{1-2} = 0.05$ $p_{1-c} = 0.09$ $p_{2-c} = 0.10$
GFR, ml/min/ 1,73 m^2 (CKD-EPI)	85.3 ± 11.5	90.3 ± 14.6	86.3 ± 9.8	$p = 0.30$ $p_{1-2} = 0.05$ $p_{1-c} = 0.09$ $p_{2-c} = 0.05$

End of the table

Parameter	Group 1 n= 50	Group 2 n= 50	Control, n= 30	p
Insulin, μIU/ml	14.3 ± 6.7	6.5 ± 2.4	4.5 ± 0.5	$p = 0.01$ $p_{1-2} = 0.001$ $p_{1-c} = 0.001$ $p_{2-c} = 0.05$
HOMA	3.5 ± 1.0	1.3 ± 0.5	1.3 ± 0.6	$p = 0.10$ $p_{1-2} = 0.03$ $p_{1-c} = 0.03$ $p_{2-c} = 0.80$
FSH, mIU/ml	8.7 ± 2.3	7.1 ± 1.9	6.7 ± 2.0	$p = 0.10$ $p_{1-2} = 0.06$ $p_{1-c} = 0.04$ $p_{2-c} = 0.05$
FLI, U.	84.3 ± 6.9	42.3 ± 4.3	39.7 ± 2.1	$p = 0.03$ $p_{1-2} = 0.01$ $p_{1-c} = 0.01$ $p_{2-c} = 0.05$
Albumin/creatinine, mg/g	10.7 ± 1.3	7.7 ± 1.2	3.0 ± 0.3	$p = 0.07$ $p_{1-2} = 0.05$ $p_{1-c} = 0.04$ $p_{2-c} = 0.05$

Note: SBP – systolic blood pressure; DBP – diastolic blood pressure; WC/HC – waist circumference/hip circumference ratio, TC – total cholesterol, LDL-C – low density lipoproteins cholesterol, HDL-C – high density lipoproteins cholesterol, TG – triglycerides, HOMA – insulin resistance index, GFR – glomerular filtration rate, ALT – alanine aminotransferase, AST – aspartaminotransferase, γ-GTP – gamma-glutamyltransferase; FSH – follicle stimulating hormone; FLI – fatty liver index; p – 5 % significance level of the differences, at which the differences were considered reliable; unrel. – the differences are statistically unreliable.

Notably, with an equal BMI in the comparison groups, in Group 1, the levels of leptin and resistin exceeded the values of Group 2. In the comparison groups, leptin levels correlated with BMI (r = 0.52 and r = 0.46), $p < 0.05$. In the MAFLD group, the level of resistin was associated with TNF-α with HOMA (r = 0.63 and r = 0.28), ALT (r = 0.52 and r = 0.50), AST (r = 0.68 and r = 0.35), GGT (r = 0.72 and r = 0.63), HDL-C (r = -0.50; r = -0.42) and fibroelastography findings (r = 0.75 and r = 0.32). In addition, the correlations of resistin with the level of VEGF (r = 0.52), TNF-α (r = 0.41) and MCP-1 (r = 0.55) were revealed. TNF-α was associated with the level of MCP-1 (r = 0.51) and VEGF (r = 0.31); IL-6 – with the level of γ-GTP (r = 0.57). In the group without MAFLD, the association of the VEGF level with HOMA-IR (r = 0.45), MCP-1 (r = 0.55) and IL-6 (r = 0.53), $p < 0.05$ was revealed.

We studied the urinary excretion of markers of subclinical kidney damage and assessed their relationship with hormonal

and metabolic parameters. Despite the equivalent level of GFR in the studied groups, we obtained significant differences in the level of urinary inflammatory cytokines of kidney damage: TNF-α (0.3 [0.2; 0.5] vs. 0.20 [0.03; 0.3] pg/ml, $p = 0.04$), MCP-1 (125.5 [83.5; 155.8] vs. 92.3 [39.5; 142.7] pg/ml, $p = 0.02$), VEGF (124.3 [75.4; 255.3] vs. 105.8 [64.2; 154.8] pg/ml, $p = 0.04$), IL-6 (0.82 [0.4; 2.7] vs. 0.43 [0.04; 1.3], pg/ml, $p = 0.01$), cystatin C (44.7 [30.7; 97.5] vs. 35.6 [18.9; 87.3] ng/ml, $p = 0.04$), β_2-microglobulin (1.1 [0.5; 1.7] vs. 0.6 [0.2; 1.2] pg/ml, $p = 0.04$).

In the MAFLD group, the urinary excretion of cytokines and markers of early renal dysfunction exceeded the values of the group without MAFLD. In the studied groups we determined the corresponding associations of urinary cystatin C with the level of MCP-1 ($r = 0.53$ and $r = 0.47$), VEGF ($r = 0.72$ and $r = 0.73$), β_2-microglobulin ($r = 0.59$ and $r = 0.65$), IL-6 ($r = 0.63$ and $r = 0.54$). In the MAFLD group, we obtained an association with the level of resistin and uric acid ($r = 0.48$ and $r = 0.36$), $p < 0.05$. In addition, the associations of β_2-microglobulin with BMI ($r = 0.27$), HOMA-IR ($r = 0.39$), resistin ($r = 0.48$), creatinine ($r = 0.52$), TG ($r = 0.35$), urinary MCP-1 ($r = 0.72$), IL-6 ($r = 0.69$), and uric acid ($r = 0.72$), $p < 0.05$ were revealed. There were no significant associations in the group without MAFLD. In the group with MAFLD urinary IL-6 was associated with BMI ($r = 0.28$), WC/HC ratio ($r = 0.31$) uric acid level ($r = 0.56$), urinary MCP-1 ($r = 0.74$) and has a negative correlation with HDL-C ($r = -0.52$) $p < 0.05$.

Fatty liver disease produces a large number of hormone-like active substances, one of which is resistin. The expression of resistin is stimulated by inflammatory cytokines, while resistin itself enhances the formation of proinflammatory cytokines by macrophages [8]. A number of authors have shown that suppression of resistin at the genetic level restores tissue sensitivity to insulin and improves glucose homeostasis [9]. According to literature data, about 25 % of circulating IL-6 is synthesized by white adipose tissue. It has been stated in the literature that changes in the content of IL-6 in kidney tissue play an important role in the progression of CKD. VEGF is produced by macrophages and endotheliocytes, and serves as a marker of endothelial damage and a stimulator of fibrogenesis. It has been proven that an increase in the serum level of VEGF is associated with the progression of insulin resistance, enthelial dysfunction, and the development of NAFLD [10]. VEGF also plays a significant role in the differentiation and proliferation of mesangial cells; it has been proven that excessive production of VEGF contributes to the development of nephrosclerosis [11]. An association of increased TNF-α production with an accelerated rate of decrease in glomerular filtration rate and the development of cardiovascular pathology and metabolic diseases has been established in a number of publications [12]. In modern literature, much attention is paid to the study of MCP-1 in blood and urine in patients with metabolic diseases and CKD [13–15]. In our study, se-

rum and urinary levels of IL-6, MCP-1, VEGF and TNF-α in the groups with a combination of obesity and MAFLD were higher compared to the group with obesity without MAFLD. In the group with MAFLD, the association of blood and urine cytokines with the HOMA index, resistin, uric acid, cystatin C and β_2-macroglobulin was obtained, whereas in the obesity group without MAFLD, these associations were not revealed. Thus, it can be stated that obesity in combination with MAFLD contributes to endothelial dysfunction and activation of subclinical inflammation, causing a damaging effect on the glomerular and tubular apparatus of the kidneys.

Conclusion

1. Resistin can be considered as an unfavorable marker of cardio-metabolic disorders in people with MAFLD.

2. The association of markers of subclinical inflammation and endothelial dysfunction with markers of early renal dysfunction in women of reproductive age with MAFLD, established during the study, allows us to expand the understanding of the cardio-reno-metabolic continuum.

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