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Proinflammatory interleukins 2, 6 and tumor necrosis factor alpha in patients with hypertension and diabetes mellitus depending on the presence of metabolic-associated liver steatosis

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Abstract. Background. *Lack of information about proinflammatory interleukins (IL) and tumor necrosis factor alpha (TNFα) levels in case of metabolic-associated liver steatosis (MALS) and their roles in its progression to steatohepatitis are key reasons for the relevance and actuality of our study. The purpose: to evaluate proinflammatory interleukins 2, 6, and TNFα levels in concomitant liver steatosis.* ***Materials and methods.*** *Thirty-five patients with hypertension stage II–III, type 2 diabetes mellitus were examined. All of them were treated on an outpatient basis according to the guidelines of the Ministry of Health of Ukraine and the Declaration of Helsinki. Participants were divided into the main group with MALS (n = 24, males 45.8 %, females 54.2 %; average age 55.83 ± 0.89 years) and the control group without steatosis (n = 11, males 54.5 %, females 45.5 %; average age 53.00 ± 1.55 years). In addition to standard parameters, levels of IL6, IL2, TNFα, selectin, resistin, insulin, C-peptide, glycated hemoglobin, non-esterified fatty acids were evaluated, and some indexes were calculated, including triglyceride-glucose index and Castelli indexes I and II. Results were processed statistically, with significance level of p < 0.05.* ***Results.*** *Although MALS is not followed by qualitative differences in proinflammatory IL2, IL6 and TNFα compared to no steatosis, the risk of TNFα elevation was 5 times higher in patients with MALS (odds ratio 5.08; 95% confidence interval 1.02–25.17). An increase in IL2 and TNFα is unfavorable for patients with MALS, it can be considered as a marker of steatosis progression to steatohepatitis, as it is associated with transaminase activation, endogenous intoxication, lipid distress and glucose intolerance. IL6 was rather lower in patients with MALS compared to those without steatosis, but its growth was exponential and proceeded simultaneously to IL2 and TNFα.* ***Conclusions.*** *MALS was not associated with significant changes in IL2, IL6 and TNFα compared to no steatosis, but their elevation can be criteria for transformation into steatohepatitis due to the activation of transaminases, inflammation, endogenous intoxication, lipid distress, glucose intolerance.*

Keywords: *diabetes mellitus; interleukin-2; interleukin-6; tumor necrosis factor alpha; metabolic-associated liver steatosis*

Introduction

Metabolic dysfunction-associated fatty liver disease (MAFLD), which gradually progresses from metabolic-associated liver steatosis (MALS) to steatohepatitis and liver cirrhosis, is a worldwide pandemic. It affects one third of adult population in the developed countries [1] and causes a decrease in the effectiveness of treatment for other diseases due to the high metabolic activity of the liver. It was recently discovered that liver itself is an endocrine-paracrine organ, which secrets regulatory substances hepatokines, including those with marked pro-inflammatory activity, particularly interleukins, tumor necrosis factor alpha (TNFα), and more commonly known orosomucoids, C-reactive protein, fibrinogen.

Interleukin 2 (IL2) is produced by CD4+ and CD8+ T-lymphocytes, some B-lymphocytes, and dendritic antigen-presenting cells, located in liver tissue, providing immunological response to multiple blood antigens. It adjusts leukocyte activity and immune system function (prevents

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autoimmunological reactions, controls T-lymphocyte subpopulations ratio, increases activity of natural killer cells and cytotoxic T-lymphocytes), but its precise role in MAFLD origin and progression remains unknown. It was outlined that in patients with non-alcoholic steatohepatosis, the quantity of IL2 receptors on cell surface rises simultaneously with tissue fibrosis development. Thuswise, level of IL2 receptors can be used as a MAFLD marker [2] or as a marker of advanced cirrhosis (contrary to mild or no cirrhosis) in patients with MAFLD [3]. In a trial, IL2 induced minor increase in lactate production in isolated hepatocyte suspension [4].

IL6 is produced by macrophages, including those located in liver parenchyma; however, its role in MAFLD pathogenesis is also unclear. In experiment, IL6 affected isolated hepatocyte suspension in a similar way as IL2, inducing less noticeable lactate increase, which is a marker of gluconeogenesis activation [4], specifically IL6 instead of TNFα enhanced lipogenesis in culture of rat hepatic cells [5].

TNFα is produced by macrophages (including liver parenchyma macrophages) and by a variety of other cells (lymphocytes, cardiomyocytes, adipocytes, hepatocytes, fibroblasts, and neurons) in response to bacteria lipopolysaccharide and IL1 elevation. It stimulates insulin resistance, maintains immune response, induces apoptosis, causes fever and cachexia, regulates anti-inflammatory response alongside with IL6, activates pro-inflammatory hepatokine synthesis in liver (orosomucoids, C-reactive protein, fibrinogen) and in excessive amount it can trigger cytokine storm and shock [6]. Lack of information about ILs and TNFα levels in case of MALS and their role in its progression to steatohepatitis are key reasons for the relevance and actuality of our study.

The purpose of study was to evaluate proinflammatory interleukins 2, 6, and TNFα levels in concomitant liver steatosis.

Materials and methods

Thirty-five patients with hypertension II–III stage, grade 2–3, compensated heart failure I–II functional class according to NYHA classification, type 2 diabetes mellitus were examined. All of them were treated on an outpatient basis according to the guidelines of the Ministry of Health of Ukraine and the Declaration of Helsinki.

Participants were divided into two groups: the main group with MALS (n = 24, males 11/45.8 %, females 13/54.2 %; average age 55.83 ± 0.89 years) and the control group without steatosis (n = 11, males 6/54.5 %, females 5/45.5 %; average age 53.00 ± 1.55 years). Groups were identical in gender, age, and hypertension duration (9.83 ± 2.09 and 10.10 ± 3.25 years). At the same time, it turned out that in 19 (79.2 %) patients with MALS, hypertension was associated with chronic forms of coronary artery disease (CAD) with duration of 1.76 ± 0.43 years, whereas in control group, no patients had CAD ($p < 0.05$). Duration of type 2 diabetes was 3.37 ± 0.55 years in main group; in controls, it was newly diagnosed ($p < 0.05$).

Although according to body mass index, patients with MALS were obese and controls were overweight (33.47 ± 1.00 and 28.72 ± 1.09 kg/m^2; $p < 0.05$), both groups were identical in nature of obesity and waist-to-hip ratio (1.03 ± 0.05 and 0.98 ± 0.02; $p > 0.05$), which allows us to evaluate adipose tissue development as analogical. In addition to standard liver function parameters, endogenous intoxication parameters (creatinine, urea), lipid and carbohydrate metabolism, insulin, C-peptide, glycated hemoglobin (HbA1c) and oral glucose tolerance test, non-esterified fatty acids, IL6, IL2, TNFα, selectin, resistin levels were evaluated and variety of complex indexes was calculated, including De Ritis ratio, triglyceride-glucose index (TyG = TG (mmol/l) × fasting glucose (mmol/l)) / 2 [7] and two Castelli risk indexes (I — total cholesterol (TC)/high-density lipoproteins (HDL); II — low-density lipoproteins (LDL)/HDL). Results were processed statistically, with admitted significance level of $p < 0.05$.

Results

In the examined patients, MALS presence did not interfere with IL2 level, which ranged within 0.56–15.1 pg/ml and was 6.52 ± 0.67 pg/ml in patients with MALS and 5.67 ± 0.54 pg/ml in those without steatosis ($p > 0.05$). Level of IL2 in MALS correlated directly with adipocytokine resistin ($r = 0.62$; $p < 0.01$) and cytokine TNFα levels ($r = 0.54$; $p < 0.05$). It also had negative correlation with TyG ($r = –0.46$; $p < 0.05$) — criteria of insulin resistance [8], pre-clinical atherosclerosis [9], atherosclerotic plaques stability in carotid and intracranial arteries [10] and MAFLD in general [11].

In patients with concomitant MALS, IL2 level above average (9.57 ± 0.58 pg/ml) was associated with significant differences: shorter CAD duration (0.78 ± 0.17 vs 2.46 ± 0.68 years), but higher levels of both transaminases (aspartate aminotransferase: 46.46 ± 6.79 vs 31.84 ± 1.85 mmol/h/l; alanine aminotransferase: 50.82 ± 7.39 vs 37.61 ± 1.95 mmol/h/l), less pronounced endogenous intoxication syndrome (creatinine: 81.37 ± 3.56 vs 94.56 ± 5.02 μmol/l), $p < 0.05$ for all findings, as well higher level of TNFα (8.94 ± 1.34 vs 5.63 ± 1.10 pg/ml; $p = 0.07$). Hence, higher level of IL2 typical for patients with shorter history of concomitant CAD, but more active, although short-time inflammation, as we can assume from IL2 and TNFα levels itself, can be considered as an acute because it was not followed by endogenous intoxication syndrome.

According to conducted correlational analysis, further growth of IL2 will be associated with increased resistin ($r = 0.74$; $p < 0.05$) and decreased selectin levels ($r = –0.64$; $p < 0.05$), along with lipid distress aggravation (TC: $r = 0.74$; Castelli index I: $r = 0.96$) and carbohydrate intolerance (postprandial glucose measurement: $r = 0.66$); $p < 0.05$ for all of the above. Whereas increased level of IL2 was associated with significantly higher pro-inflammatory TNFα, its correlation patterns in the presence of high IL2 have also been indicated. An increase in TNFα was followed by endogenous intoxication syndrome (creatinine: $r = 0.86$; $p < 0.01$) and lipid distress (HDL: $r = –0.89$; Castelli index I: $r = 0.89$; $p < 0.05$ for both of them), as well as rise of resistin level ($r = 0.68$; $p < 0.05$), which is considered to be the marker of obesity, inflammation, and advanced liver tissue fibrosis [12].

Discussion

Levels of TNFα in patients with MALS and without steatosis were similar (7.07 ± 0.90 and 6.01 ± 0.84 pg/ml; $p > 0.05$) and remained within the normal range (up to 10.0 pg/ml), concentrations fluctuated from 1.32 to 14.5 pg/ml, which corresponds to literature-based data, where its increase is described as a marker of steatohepatitis [13, 14] or advanced fibrosis in case of MAFLD [15, 16].

TNFα concentration, in addition to IL2, had direct correlation with resistin levels in the examined patients ($r = 0.50$; $p < 0.05$). Nevertheless, in MALS, the risk of TNFα elevation was 5 times higher (OR 5.08; 95% CI 1.02–25.17). According to absolute value of determined parameters, patients with higher (11.24 ± 0.96 pg/ml) and lower (3.87 ± 0.38 pg/ml) than average levels of TNFα did not differ from each other.

Correlational analysis has shown that among patients with above average TNFα level, its further growth would be associated with endogenous intoxication syndrome (urea: $r = 0.78$; $p < 0.05$). It also correlates directly with resistin levels (creatinine-resistin: $r = 0.71$; $p < 0.05$) that can be considered as a marker of MALS progression to steatohepatitis. Whereas increased resistin level leads to elevation of C-peptide and TC ($r = 0.63$; $p = 0.07$ and $r = 0.77$; $p < 0.05$), markers of carbohydrate and lipid metabolism impairment. It means that MALS is characterized by normal TNFα level, but 5 times higher probability of its elevation, which in turn would be associated with development of endogenous intoxication, lipid distress, glucose intolerance and progression of steatosis into steatohepatitis.

In the examined patients, presence of steatosis did not significantly influence IL6 level (3.22 ± 0.67 and 3.23 ± 0.84 pg/ml; $p > 0.05$), its concentration in patients with MALS was characterized by a great amplitude (0.47–13.7 pg/ml) and did not correlate with other parameters. Interestingly, in most cases (79.2 %), level of this cytokine was below average, whilst elevated in 20.8 % ($p < 0.05$), but in that case, it was 2.4–4.2 times above limit. One-fifth of patients with increased IL6 (8.60 ± 1.67 pg/ml) was characterized by shorter hypertension duration (4.40 ± 1.50 vs 11.26 ± 2.52 years; $p < 0.05$), less intense course of endogenous intoxication syndrome (creatinine: 76.10 ± 2.10 vs 93.09 ± 4.14 μmol/l; $p < 0.01$; urea: 4.16 ± 0.33 vs 5.27 ± 0.39 mmol/l, $p < 0.05$) and better lipid profile (LDL: 2.30 ± 0.33 vs 3.91 ± 0.53 mmol/l; TC: 4.67 ± 0.31 vs 5.98 ± 0.48 mmol/l; $p < 0.05$ for both; Castelli index II: 1.44 ± 0.26 vs 3.16 ± 0.49; $p < 0.01$).

In our opinion, low IL6 level is unfavorable, as it is observed in case of long-term hypertension and is followed by distress of lipid metabolism. In patients with MALS and IL6 concentrations above average, among all measured cytokines, only TNFα correlated significantly with creatinine ($r = 0.94$; $p < 0.05$) and non-esterified fatty acids ($r = –0.97$; $p < 0.01$).

Amidst patients with IL6 level below average, its concentration was significantly associated with elevated production of other cytokines, IL2 ($r = 0.67$; $p < 0.01$), TNFα ($r = 0.66$; $p < 0.05$) and resistin ($r = 0.63$; $p < 0.05$), which were also connected significantly (IL2-resistin: $r = 0.60$; IL2-TNFα: $r = 0.60$; resistin-TNFα: $r = 0.51$), on the background of better carbohydrate profile (TyG: $r = –0.68$; $p < 0.05$; C-peptide: $r = 0.94$); all $p < 0.05$.

MAFLD is a growing global health burden among the population with high susceptibility to obesity and insulin resistance [17]. The most effective prevention strategy for MAFLD is lifestyle modification [18]. Considering the prevalence and its impact, several novel methods, including therapeutic and surgical approaches, are currently under investigation [19]. Pharmacological interventions, such as treatment with antidiabetic medications, and anti-obesity drugs, can be considered for MAFLD patients but should be chosen wisely on a case-to-case basis. In addition, bariatric surgery aimed to obtain durable weight loss is an option for MAFLD patients who either fail medical management or have associated comorbidities. Novel approaches in drug delivery would be ideal for managing MAFLD in the future [20].

Conclusions

Although MALS is not followed by qualitative differences in proinflammatory IL2, IL6 and TNFα compared to no steatosis, the risk of TNFα elevation was 5 times higher in patients with MALS (OR 5.08; 95% CI 1.02–25.17). An increase in IL2 and TNFα is unfavorable for patients with MALS, it can be considered as a marker of steatosis progression to steatohepatitis, as it is associated with transaminase activation, endogenous intoxication, lipid distress and glucose intolerance. IL6 was rather lower in patients with MALS compared to those without steatosis, but its growth was exponential and proceeded simultaneously to IL2 and TNFα.

Further studies perspectives: to study levels of these cytokines in other metabolic-associated liver diseases.

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Прозапальні інтерлейкіни-2, -6 і фактор некрозу пухлини альфа в пацієнтів з артеріальною гіпертензією та цукровим діабетом залежно від наявності метаболічно-асоційованого стеатозу печінки

Резюме. ***Актуальність.*** Недостатня кількість інформації про вміст прозапальних інтерлейкінів (ІЛ) і фактора некрозу пухлини альфа (ФНП-α) за умов метаболічно-асоційованого стеатозу печінки (МАСП) та їхньої ролі в процесі переходу в стеатогепатит зумовили доцільність та актуальність нашого дослідження. ***Мета:*** оцінити вміст прозапальних ІЛ-2, ІЛ-6 та ФНП-α за умов супутнього МАСП. ***Матеріали та методи.*** Обстежено 35 пацієнтів з артеріальною гіпертензією та цукровим діабетом 2-го типу, яких лікували амбулаторно відповідно до стандартів МОЗ України та Гельсінської декларації. Учасники були поділені на основну групу з МАСП (n = 24, чоловіки 45,8 %, жінки 54,2 %; середній вік 55,83 ± 0,89 року) та контрольну групу без стеатозу (n = 11, чоловіки 54,5 %; жінки 45,5 %; середній вік 53,00 ± 1,55 року). Крім стандартних параметрів, оцінювали рівні ІЛ-6, ІЛ-2, ФНП-α, селектину, резистину, інсуліну, С-пептиду, глікованого гемоглобіну, вільних жирних кислот, розраховували тригліцерид-глюкозний індекс та індекси Castelli I, II. Результати опрацьовано статистично. ***Результати.*** Хоча при МАСП не спостерігалося відмінностей у рівнях прозапальних ІЛ-2, ІЛ-6 та ФНП-α порівняно з пацієнтами без стеатозу, особи з МАСП мали в 5 разів вищу ймовірність зростання ФНП-α (відносний ризик 5,08; 95% довірчий інтервал 1,02–25,17). Несприятливим для пацієнтів із МАСП було збільшення ІЛ-2 і ФНП-α, яке можна вважати маркером переходу стеатозу в стеатогепатит, оскільки це асоціюється з активацією трансаміназ, ендогенною інтоксикацією, ліпідним дистресом та непереносимістю глюкози. Вміст ІЛ-6 у пацієнтів із МАСП був дещо нижчим, ніж в осіб без стеатозу, однак його зростання було експоненційним і відбувалось паралельно ІЛ-2 та ФНП-α. ***Висновки.*** Наявність МАСП не викликала істотних змін ІЛ-2, ІЛ-6, ФНП-α, проте зростання їхнього рівня можна вважати несприятливим чинником переходу в стеатогепатит, оскільки воно було пов'язано з активацією трансаміназ, системним запаленням, ендогенною інтоксикацією, ліпідним дистресом та непереносимістю глюкози.

Ключові слова: цукровий діабет; інтерлейкін-2; інтерлейкін-6; фактор некрозу пухлин альфа; метаболічно-асоційований стеатоз печінки