CIRCULATING LEVELS OF TUMOR NECROSIS FACTOR-ALPHA IN TYPE 2 DIABETES MELLITUS PATIENTS WITH NON-ALCOHOLIC FATTY LIVER DISEASE TAKING INTO ACCOUNT THE VASCULAR COMPLICATIONS*

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Non-alcoholic fatty liver disease (NAFLD) is a clinicopathological change characterized by the accumulation of triglycerides in hepatocytes and has frequently been associated with obesity, type 2 diabetes mellitus (T2D), hyperlipidemia, and insulin resistance (IR) [1]. NAFLD is strongly associated with hepatic IR, inflammation and fibrosis. NAFLD is not only associated with metabolic syndrome but is also an independent risk factor for cardiovascular disease (CVD), with CVD accounting for majority of deaths in patients with this disease [2, 3]. The most important focus of the NAFLD-related chronic diseases during the last 10 years has involved chronic liver disease, CVD and T2D; e. g., a recent meta-analysis showed that NAFLD increased overall mortality by 57 % mainly from liver-related and CVD causes, and increased risk of incidents T2D by approximately two fold [4]. Dyslipidemia, IR, increased production of proinflammatory cytokines, low adiponectin, high PAI-1 levels, hypertension, and hyperglycemia are main factors that lead to NAFLD, further aggravate the course of NAFLD, and accelerate the progress of atherosclerosis and the development of CVD [5]. Collectively, all the above findings support the notion that there is a causal, bi-directional link between NAFLD and T2D [6]. It is well-known that the balance between pro- and anti-
inflammatory cytokines is fundamental in the control of systemic and hepatic insulin action, and as a consequence, in the development of NAFLD [7]. Adipose tissue has been recognized as an active endocrine organ and a main energy store of the body [8].

Tumor necrosis factor-alpha (TNF-α) is a proinflammatory cytokine and its expression is hugely increased in the fat cells of obese human subjects and patients with IR. This cytokine acts as the link between systemic inflammation, IR and obesity [9], which plays an important role in the development of T2D. However, there are reports about absence of relationship between circulating TNF-α, obesity and T2D [10].

The question remains about the role of proinflammatory cytokines, in particular TNF-α, in initiating and maintaining inflammation at various stages of development of NAFLD, and the data presented in the literature are few and contradictory. Therefore, the purpose of our work was to study the circulating levels of TNF-α in patients with type 2 diabetes and to determine the nature of vascular complications in the presence and absence of NAFLD.

MATERIALS AND METHODS

The general population consisted of patients with T2D with long duration of the disease against the background of metabolic syndrome, with varying degrees of glycemic control and hepatic homeostasis disorders, in the absence of renal failure, in the age range of 28 to 80 years. For the analysis, 146 people were selected: 95 of them were type 2 diabetics in the presence of NAFLD and 51 patients with T2D without NAFLD. The data were collected through a standard questionnaire. All patients were interviewed regarding a full medical history that included age, sex, occupation, duration of diabetes, mode and duration of treatment, presence of any associated illness, surgical history, personal history of smoking/alcohol/drug abuse, dietary habit and family history of diabetes. Controls (n = 21) were individuals with no clinically significant abnormal physical findings. None of the controls had any personal history of diabetes at the time of blood donation, which was ascertained with a questionnaire completed by each healthy volunteer. All cases and controls signed an informed consent for clinical and biochemical studies and the protocols were approved by the institutional review board of SI «V. Danilevsky Institute of Endocrine Pathology Problems of NAMS of Ukraine». Cases and controls from study were all Caucasoids and residents of Kharkiv region (Ukraine). The cases were clinically and biochemically confirmed as T2D. The diagnosis NAFLD was verified in accordance with the recommendations of the American Gastroenterological Association (AGA) and the American Association for the Study of liver disease based on the clinical course of the disease, lipid and carbohydrate metabolism, activity of alaninaminotransferase (ALT), aspartataminotransferase (AST), ratio ALT/AST and sonographic examination [26]. Nutritional status was assessed by measuring weight, height and abdominal circumference using well established techniques. Statistical analysis was performed using parametric and nonparametric methods. To compare the indices with normal distribution Student’s t-test was used and for comparison variables with abnormal distribution Mann-Whitney’s U-test was used. The data are presented as mean ± SEM.

RESULTS AND DISCUSSION

Compared to control subjects, T2D patients were characterized by a significant (p<0,05–0,001) increase in body mass index (BMI), increased levels of free fatty acids, triglycerides (TG), TNF-α, insulin, HOMA-IR indexes and decreased insulin sensitivity (QUICKI). Patients with T2D and NAFLD have a higher BMI (35.10 ± 0.77 kg/m²) than type 2 diabetic patients without NAFLD (32.13 ± 0.82 kg/m²) (p<0.001). The waist-to-hip ratio (WHR) among patients with T2D and NAFLD (0.99 ± 0.01) is higher (p<0.05), than among patients with T2D without NAFLD (0.96 ± 0.01). In diabetic patients, an increase in the HOMA-IR index was verified in the presence of NAFLD (9.86 ± 1.44) compared to the group of patients with T2D, uncomplicated NAFLD (6.65 ± 0.62), (p<0.05). The increase
in the indexes detected during the examination of the patients proves the presence of NAFLD-related pathogenic factors that adversely affects tissue sensitivity to insulin. In patients with T2D and NAFLD in comparison with non-NAFLD patients with T2D, features of dyslipidemia with a significant increase in TG content (3.96 ± 0.57 mmol/l vs. 2.22 ± 0.15 mmol/l) were established (p < 0.05). It was found that the average level of TNF-α in patients with T2D was 3-fold higher as compared to the control group (5.47 ± 3.44 pg/ml, p < 0.05). Stratification of the diabetic population on the base of the presence/absence of NAFLD shown a more pronounced increase in circulating levels of TNF-α in the presence of NAFLD (20.36 ± 4.81 pg/ml vs. 10.05 ± 1.62 pg/ml, p < 0.05) which substantiates this parameter utility for further applications as a diagnostic marker for the aforementioned complication.

It was found that the level of TNF-α in this cohort of patients (in the presence of NAFLD) was associated with body weight. Thus, in the group with elevated BMI (26–29 kg/m²) TNF-α level was (17.98 ± 5.34) pg/ml, while in the group with BMI ≥ 30 it was (33.58 ± 5.90) pg/ml (5.47 ± 3.44) pg/ml in the control group, p < 0.05. It is known that with the development of obesity there is not only an increase in the size and number of adipocytes (hypertrophic/hyperplastic expansion of adipose tissue), but also a change in their functional activity, which promotes the development of clinical and metabolic changes associated with obesity. The increase in the severity of IR in patients with T2D complicated by NAFLD, is accompanied by an increase in the activity of the pro-inflammatory link of the cytokines presented by TNF-α, which can be considered as a trigger of the complication. Despite a fairly large number of studies of the NAFLD development mechanisms, there is no clear idea of the inflammatory cytokine dependence on the NAFLD stage. Thus, the study of the TNF-α role in the pathogenesis and progression of NAFLD represents an undoubted interest.

It is known that IR and arterial hypertension are two interrelated events that lead to atherosclerotic vascular damage. Hyperinsulinemia is pathogenically associated with the arterial hypertension development, because high levels of insulin increase the activity of the sympathetic nervous system, thereby increasing cardiac output and peripheral vascular resistance. Hyperinsulinemia stimulates the proliferation of the vascular smooth muscle cells, which leads to an increase in vascular rigidity, as well as stimulates the activity of the renin-angiotensin system, increases endothelin production [11]. It is believed that higher levels of systolic and diastolic blood pressure are recorded in patients with NAFLD, but we did not find a statistically significant difference between groups in the presence and absence of NAFLD (systolic pressure (142.20 ± 3.84) mm Hg, diastolic pressure (92.30 ± 3.24) mm Hg for NAFLD vs. systolic pressure (142.86 ± 1.86) mm Hg, diastolic pressure (87.17 ± 2.86) mm Hg for non-NAFLD, p>0.05). In our study, the presence of arterial hypertension (AG) was found in more than half of obese patients. Hypertension was also significantly more common in the group of patients with NAFLD (76.56 % vs. 64.71 % in the absence of NAFLD), but the statistical significance of this difference was not proved, perhaps due to the small sample size.

Many studies have shown the relationship between NAFLD and hyperlipidemia. We found significant differences (p < 0.01 – p < 0.001) in TG and the other dyslipidemia parameter levels between patients with and without NAFLD. Thus, in 85.19 % of patients with T2D, in the presence of NAFLD there was an increase in the level of total cholesterol, 62.22 % — LDL cholesterol, 61.81 % — level of triglycerides, and in 100 % of patients was revealed decrease in HDL cholesterol. At the same time, only in 29.41 % of patients with T2D without NAFLD there was an increase in the level of total cholesterol, 17.64 % — LDL cholesterol, 41.17 % — level of triglycerides, and in 47.05 % of patients was reduced HDL cholesterol. Accordingly, our data indicate a significantly enhanced risk of cardiovascular complications in the examined diabetic patients with NAFLD.

In several recent studies there was a high risk of coronary heart disease (CHD) in patients with NAFLD. In our study, 67.37 % of patients with T2D were diagnosed with CHD. It was found that coronary artery disease was observed in 63.2 % of patients with NAFLD
and in 68.6% of patients who had no concomitant liver disease \((p > 0.05)\). Our data do not coincide with the results of a study conducted by Wong V. W. et al. (2011), wherein, particularly, the clinical implications of coronary angiography in patients with NAFLD were analyzed; the endpoint combines cardiovascular mortality, nonfatal myocardial infarction and the need for coronary intervention. There were 612 patients participated in the Wong’s study, 356 (58.2%) patients had ultrasound signs of NAFLD, 318 (52.0%) participants had elevation of ALT, and 465 (76.0%) patients had CHD (the CHD was observed in 84.6% of NAFLD patients and in 64.1% non-NAFLD patients, \(p < 0.001\)). Having made an amendment to the demographic indicators, the authors established a direct relationship between the presence of NAFLD and the development of coronary heart disease, elevation of ALT and the formation of coronary artery disease. Having analyzed the obtained data, the authors of the study concluded that the presence of NAFLD can provoke the development of coronary artery disease. However, according to the authors, «fatty liver» cannot «predict» CHD and mortality in patients with established coronary artery disease [12]. On the other hand, experimental data with respect to the myocardium morphology of young animals with the alimentary obesity model indicated the development of circulatory disorders (plethora and thrombosis of vessels, diapedesis hemorrhages, myocardial hypertrophy, interstitial and perivascular edema, focal cardiosclerosis), which results in the fatty myocardial dystrophy [13]. Explanation the reasons for the discrepancy between our research data and Wong’s ones may consist of the fact that a genetically different contingent of patients was examined. It is known that NAFLD can be a risk factor for the development of T2D and cardiovascular disease. It has been shown by Gastaldelli A. et al. (2009) that NAFLD increases the risk of CHD occurrence irrespective of other predictors and manifestations of metabolic syndrome. [14]. Our study included patients who already had T2D in the presence and absence of NAFLD, while the work of foreign authors was a prospective study involving patients with NAFLD and without liver disease who had undergone coronary angiography. Consequently, differences in the frequency of CHD in patients are also associated with long-term T2D in our cohort of patients, but, as we know, T2D is a lesion of the macro- and microvasculature. Pathogenic mechanisms of close relationship between T2D and coronary artery disease, which predetermine the early development and aggressive course of coronary atherosclerosis, are still not completely clear and actively studied. Among them a significant role is given to oxidative stress. As it is known, hyperglycemia in uncontrolled diabetes is the cause of metabolic dysfunction, auto-oxidation of glucose, non-enzymatic glycosylation of proteins, and activation of glucose metabolism through the polyol pathway with an increase in the manifestation of oxidative stress [15].

Thus, the main explanation for the same incidence of coronary artery disease in patients with T2D in the presence and absence of NAFLD is the independent contribution of T2D to the overall risk of CVD.

The participation of cytokines including TNF-α and endothelial dysfunction in the progression of vascular pathology has been established. At the same time, TNF-α is not sufficiently defined in the formation of cardiovascular risk under T2D in combination with NAFLD. The obtained results indicate that the proinflammatory cytokine TNF-α can be considered as a marker of cardiovascular risk, since the level of this cytokine is increased in patients with hypertension and high body mass and abdominal obesity [16–18]. It is possible that cytokines can play a key role in the progression of NAFLD, since TNF-α and other cytokines cause not only damage of hepatocytes, but also the development and progression of IR and endothelial dysfunction. It is known that TNF-α activates the nuclear transcription factor kappa B (NF-kB) in adipocytes and hepatocytes, which leads to increased phosphorylation of the type I insulin receptor, a violation of insulin binding to the receptor, a decrease in the activity of glutathionetransferase 4 and phosphoinositol-3-kinase and, thus, to reduce the uptake and utilization of glucose by cells, the elevation of hyperglycemia and the development of IR and oxidative stress. The activation of NF-kB also stimulates the production of inducible NO-synthase, contributing to the
development of inflammatory reaction in the vascular wall, adhesion of the monocytes to the endothelium and the entire cascade of oxidative stress. Under the influence of TNF-α, smooth muscle and endothelial cells of blood vessels increase the production of monocyte chemotaxis protein 1, which plays an important role in the development of microcirculatory disorders. TNF-α also promotes expression and synthesis of the Bcl-2 protein that activates hepatocyte apoptosis [19–21].

However, studies on the contribution of TNF-α to the development of cardiovascular complications in patients with T2D and NAFLD are ambiguous. Stratification of the diabetic patients in the presence and absence of vascular complications shown a significant increase (p < 0.05) in circulatory levels of TNF-α compared to control subjects in both subgroups of patients, with greater emphasis on its severity in association with clinically manifested macroangiopathies-CVD and hypertension in the presence of NAFLD (see Table 1, Table 2).

An analysis of the TNF-α level in T2D patients with and without NAFLD, as well as in the presence and absence of vascular complications was demonstrated significant changes. Thus, in patients with NAFLD and CVD the mean TNF-α level was greater, than in the patients with T2D without NAFLD, but in the presence of CVD (p < 0.05, see Table 1, 2). It was found the difference between TNF-α levels in non-NAFLD diabetic patients with different types of vascular complications (p < 0.05 – p < 0.02). There were almost 2-fold higher TNF-α levels in patients with T2D and NAFLD regardless of vascular complication type (p < 0.05, see Table 1). In general, the group of patients without the liver disease had lower levels of TNF-α, but the lowest levels of TNF-α were noted in patients with T2D without the liver or vascular complications (p < 0.05, see Table 2).

Thus, the absence of significant differences in the concentration of circulating proteins at the background of macro/microvascular complications with IR and NAFLD confirms the leading influence of IR and dysglycemia on the above parameters of the chronic inflammatory process in patients with T2D complicated by

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<th>The nature of the complication</th>
<th>TNF-α level, pg/ml</th>
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<td>+</td>
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<td>Ischemic heart disease</td>
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<td>Hypertension</td>
<td>16.81 ± 2.40</td>
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<tr>
<td>Retinopathy</td>
<td>17.42 ± 2.13</td>
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<tr>
<td>Neuropathy</td>
<td>17.08 ± 2.32</td>
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Table 1

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<tr>
<td>Ischemic heart disease</td>
<td>10.88 ± 1.89</td>
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<tr>
<td>Hypertension</td>
<td>10.92 ± 1.76</td>
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<td>Retinopathy</td>
<td>10.93 ± 1.76</td>
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<tr>
<td>Neuropathy</td>
<td>10.31 ± 1.82</td>
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Table 2

Note:
* p < 0.02 compared to the patients with vascular complications.
NAFLD. Our data suggest the presence of additional factors that modulate the total TNF-α level in patients with T2D and NAFLD against the background of vascular complications. In the examined patients with T2D and NAFLD, a significant increase in TNF-α level was detected, regardless of the presence of concomitant vascular disease, which may be indicative of the predominant effect of IR and dysglycemia on the above-mentioned parameters of the chronic inflammatory process.

Recently published data on the development of cardiovascular disease form the view that most new biomarkers do not improve the likelihood of predicting the risk of its development when included in a model that is based on traditional risk factors [22]. At the same time, we suggest, that the found associations of such new biomarker as TNF-α level, along with other metabolic markers (e. g., BMI), and the risk of NAFLD development not only help us to understand their role in the pathogenesis of the disease, but also substantiate prospects of their use in the preventive therapy. We agree with statement, that diabetes and NAFLD are reciprocal risk factors and when they are occur together, an increasing body of data demonstrates that diabetes is more difficult to manage and that NAFLD is more likely to progress [23].

CONCLUSION

Non-alcoholic fatty liver disease is closely associated with hormonal and metabolic risk factors and markers of cardiovascular disease and type 2 diabetes and may increase the risk of development and progression of cardiovascular complications.

Stratification of the diabetic population on the base of the presence/absence of NAFLD shown a more pronounced increase in circulating levels of TNF-α in the presence of NAFLD, which substantiates this parameter utility for further applications as a diagnostic marker.

There was no significant differences in the TNF-α levels in T2D patients with NAFLD regardless macro/microvascular complications, which confirms the leading influence of hepatic insulin resistance and a possible presence of additional factors, that modulate the general level of this proinflammatory cytokine.

REFERENCE

The relationship between non-alcoholic fatty liver disease (NAFLD) and risk factors for vascular disorders and type 2 diabetes mellitus (T2D) remains the subject of discussion. Therefore, the purpose of our work was to determine the circulatory levels of tumor necrosis factor-alpha (TNF-α) in patients with T2D and to determine the nature of the effect of vascular complications in the presence and absence of NAFLD on this indicator. 146 patients with T2D aged from 28 to 80 years old (86 men / 78 women) were examined, with varying degrees of glycemic control and overweight, without renal insufficiency. 95 surveyed people had NAFLD. 21 practically healthy persons were studied as controls. Compared to controls, patients with T2D at the background of impaired glucose homeostasis were characterized by a marked increase in body mass index (BMI), increased levels of free fatty acids, triglycerides (TG), TNF-α, basal insulin, HOMA-IR indices, and decreased insulin sensitivity. It was found that the average level of TNF-α in patients with T2D (17.88±3.42 pg/ml) was 3-fold higher than in the control group — 5.47±3.44 pg/ml (p<0.05). Patients with T2D with NAFLD have a greater BMI (35.10±7.77 kg/m²) than T2D patients without NAFLD (32.13±8.92 kg/m², p<0.001). Stratification of the diabetic population on the base of the presence/absence of NAFLD showed a more pronounced increase in circulating levels of TNF-α in the presence of NAFLD (20.36±4.81 pg/ml vs 10.05±1.62 pg/ml, p<0.05), which substantiates this parameter utility for further applications as a diagnostic marker. It was found the difference between TNF-α levels in non-NAFLD diabetic patients with different types of vascular complications (p<0.05 — p<0.02). There were almost 2-fold higher TNF-α levels in patients with T2D and NAFLD regardless of vascular complication type (p<0.05). In general, the group of patients without the liver disease had lower levels of TNF-α, but the lowest levels of TNF-α were noted in patients with T2D without the liver or vascular complications (p<0.05). There was no significant differences in the TNF-α levels in T2D patients with NAFLD regardless macro/microvascular complications, which confirms the leading influence of hepatic insulin resistance and a possible presence of additional factors, that modulate the general level of this proinflammatory cytokine.

Key words: type 2 diabetes mellitus, non-alcoholic fatty liver disease, tumor necrosis factor-alpha, vascular complications.
95 обстежених мали НАЖХП. 21 практично здорову людину розглядали в якості контролю. Порівняно до контролю хворі на ЦД 2 типу за умов порушеного глукозного гомеостазу характеризувалися виразним підвищенням індексу маси тіла (IMT), зростанням рівнів вільних жирних кислот, тригліцеридів (ТГ), TNF-α, інсуліну натощак, індексів HOMA-IR та зниженням чувствительності до інсуліну. Виявлено, що середній рівень TNF-α у хворих на ЦД 2 типу (17,88±3,42 пг/мл) в 3 рази вищий, ніж у групі контролю — 5,47±3,44 пг/мл (p<0,05). Хворі на ЦД 2 типу за наявності НАЖХП мають більший IMT (35,10±0,77 кг/м², p<0,001), ніж хворі на ЦД 2 типу без наявності НАЖХП (32,13±0,82 кг/м²). Стратифікація діабетичного загалу за наявності/відсутності НАЖХП засвідчила більш виразне підвищення циркуляторних рівнів TNF-α за умов НАЖХП (20,36±4,81 пг/мл проти 10,05±1,62 пг/мл, p<0,05), що обґрунтовує доцільність використання цього показника для подальшого застосування в якості діагностичного параметру вищеозначеного ускладнення. Виявлено розбіжність між рівнями TNF-α у пацієнтів із цукровим діабетом, які не мали печеночного ураження, з різними типами судинних ускладнень (p<0,05 – p<0,02). Встановлено, що пацієнти з ЦД 2 типу за наявністю до групи без печеночного ураження мали майже в 2 рази вищі рівні TNF-α незалежно від типу судинного ускладнення (p<0,05). Найнижчі рівні TNF-α відмічені у хворих на ЦД 2 типу без супутньої патології (p<0,05). Відсутність достовірного впливу судинних ускладнень на концентрацію циркулюючого TNF-α за умов НАЖХП засвідчує провідний вплив печеночного інсулінорезистентності та можливу наявність додаткових факторів, які модулюють загальний рівень даного прозапального цитокіну.

Ключові слова: цукровий діабет 2 типу, неалкогольна жирова хвороба печінки, фактор некрозу опухолі альфа, судинні ускладнення.

ЦИРКУЛЯТОРНІ УРОВНІ ФАКТОРА НЕКРОЗА ОПУХОЛИ-α У БОЛЬНИХ САХАРНИМ ДИАБЕТОМ 2 ТИПА ПРИ НАЛИЧI НЕАЛКОГОЛЬНОЇ ЖИРОВОЇ БОЛЕЗНІ ПЕЧЕНИ С УЧЕТОМ СОСУДИСТЫХ ОСЛОЖНЕНИЙ

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Взаимосвязь неалкогольной жировой болезні печени (НАЖБП) с факторами риска сосудистой патологии и сахарного диабета (СД) 2 типа остается предметом дискуссий. Поэтому целью нашей работы было определение циркуляторных уровней фактора некроза опухоли альфа (TNF-α) у больных СД 2 типа и установление характера влияния сосудистых осложнений при наличии и отсутствии НАЖБП на этот показатель. Обследовано 146 пациентов с СД 2 типа в возрасте от 28 до 80 лет (68 мужчин / 78 женщин), с разной степенью гликемического контроля и избыточной массы тела, без почечной недостаточности. 95 обследованных имели НАЖБП. 21 практически здоровую людину розглядали в якості контролю. Порівняно до контролю хворі на ЦД 2 типу за наявністю глюкозного гомеостазу характеризувалися виразним підвищенням індекса маси тіла (IMT), ростом рівнів свободних жирних кислот, тригліцеридів (ТГ), TNF-α, інсуліна натощак, індексів HOMA-IR та зниженням чувствительності до інсуліну. Виявлено, що середній рівень TNF-α у больних СД 2 типа (17,88±3,42 пг/мл) в 3 рази вищий, ніж у групі контролю — 5,47±3,44 пг/мл (p<0,05). Больные СД 2 типа при наличии НАЖБП имели больший IMT (35,10±0,77 кг/м², p<0,001), ніж больные СД 2 типа без наличия НАЖБП (32,13±0,82 кг/м², p<0,001). Стратификация пациентов с СД 2 типа по наличию/отсутствию НАЖБП показала более отчетливое повышение циркуляторных уровней TNF-α при наличии НАЖБП (20,36±4,81 пг/мл против 10,05±1,62 пг/мл, p<0,05), что обосновывает целесообразность использования данного показателя в качестве диагностического параметра вышеуказанного осложнения. Было обнаружено наличие между уровнями TNF-α у диабетических пациентов без НАЖБП с различными типами сосудистых осложнений (p<0,05 – p<0,02). Установлено, что пациенты с СД 2 типа и НАЖБП по сравнению с группой без поражения печени имели почти в 2 раза большие уровни TNF-α независимо от типа сосудистого осложнения (p<0,05). Самые низкие уровни TNF-α отмечены у больных СД 2 типа без сопутствующей патологии (p<0,05). Отсутствие достоверного влияния сосудистых осложнений на концентрацию цирулюючего TNF-α при наличии НАЖБП свидетельствует о ведущей роли печечного инсулинорезистентности и возможном наличии дополнительных факторов, которые модулируют общий уровень данного прозапального цитокина.

Ключевые слова: сахарный диабет 2 типа, неалкогольная жировая болезнь печени, фактор некроза опухоли альфа, сосудистые осложнения.