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Level of IL-6 and IL-8 and their associations with non-alcoholic fatty liver disease in patients with type 2 diabetes

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Abstract: *non-alcoholic fatty liver disease (NAFLD) is indicated by the accumulation of lipids within the hepatocytes exceeding 5% of liver weight without excessive alcohol intake and secondary liver diseases. The efforts of many scientists worldwide are focused on improving the understanding of pathogenic processes and triggers of NAFLD progression, with an emphasis on the simultaneous study of several pathophysiological pathways to identify disorders throughout the disease spectrum. The aim was to examine the serum levels of IL-6 and IL-8 and its associative relationships with anthropometric parameters and metabolic profiles in patients with T2D, depending on the presence of NAFLD. This cross-sectional study involved 375 patients aged 40–80 with type 2 diabetes. They were divided into 3 groups. The control group included 98 T2D patients without NAFLD. The main group included T2D patients with NAFLD, which was separated into two subgroups depending on the level of transaminases: normal (group 2A, n = 150) and increased (group 2B, n = 127) transaminases group. In order to identify predictors of rapid progression of liver fibrosis in patients with T2D, a sub-analysis was conducted, which included 82 patients from group 2. We found significant relationships between the level of studied interleukins and the components of the metabolic syndrome. Both IL-6 and Il-8 levels are significantly associated with gender, duration and severity of T2D, BMI, ALT, AST and total bilirubin level in a simple logistic regression analysis. However, step-by-step multiple logistic regression analysis revealed no reliable link between both cytokines and NAFLD development. From the other hand elevated IL-8 and decreased IL-6 had a significant effect on the fibrosis progression in patients with NAFLD associated with T2D. Our study has demonstrated significant links between the level of IL-6 and IL-8 and the components of the metabolic syndrome such as obesity or transaminase activity, but not with NAFLD itself.*

Keywords: diabetes mellitus, non-alcoholic fatty liver disease, interleukin-6, interleukin-8, metabolic syndrome, insulin resistance, obesity.

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Introduction

Non-alcoholic fatty liver disease (NAFLD) is characterized by the accumulation of lipids within the hepatocytes exceeding 5% of liver weight in the absence of excessive alcohol intake and secondary causes of liver diseases (Nascimbeni et al., 2013). NAFLD ranges from simple steatosis to non-alcoholic steatohepatitis (NASH) that can have different degrees of fibrosis and progress to liver cirrhosis and hepatocellular carcinoma (Kobyliak et al., 2016). The presence of NAFLD reduces the average life expectancy. If in the general population hepatic pathology is only the 13th cause of death, then in patients with NAFLD the third (Adams et al., 2005). A large single-center retrospective study, which included 619 patients with biopsy proven NASH and follow-up period for 12.6 years, showed that 33.2% of people died or had a liver transplantation (Angulo et al., 2015).

The efforts of many scientists worldwide are focused on improving the understanding of pathogenic processes and triggers of NAFLD progression, with an emphasis on the simultaneous study of several pathophysiological pathways to identify disorders throughout the disease spectrum (Mykhalchyshyn, Kobyliak & Bodnar, 2015). The development of NAFLD involves key biological processes: impairment of carbohydrate/lipid homeostasis (Chao et al., 2019), immune activation/inflammation (Sutti & Albano, 2020), fibrosis (Yamamura et al., 2020), apoptosis (Kanda et al., 2018) and carcinogenesis (Eslami et al., 2020), which forms the basis for numerous pathophysiological diseases in an individual. The comprehensive study of these processes in patients with type 2 diabetes (T2D) is especially relevant, as the latter is the main predictor of the NAFLD (Tilg, Moschen & Roden, 2017). Another important point is the identification of non-invasive biomarkers of fibrogenesis – evaluation of the liver's response to new treatments, as well as on-going evaluation of the rate of progression / regression and prognosis of the end result (histological or clinical) (Loomba, & Adams, 2020).

Interleukin-6 (IL-6) is one of the main macrophage pro-inflammatory and prodiabetic cytokines with a strong immunosuppressive effect (Allen & Febbraio, 2010), is directly related to obesity because it is produced by adipocytes and is a predictor of T2D. In 2013, a meta-analysis was published to study the level of IL-6 in peripheral blood in pre-diabetes and T2D. Totally 10 prospective studies, which included 19,709 participants were analyzed. A significant increase for IL-6 levels was observed. In addition, it has been shown that IL-6 elevation occur long before the onset of T2D and may be a reliable marker of disease development (Bowker et al., 2020). In patients with T2D and metabolic syndrome there is a doubling of two different mechanisms of entry of this cytokine into the circulation, which is confirmed by recent study (Sattar et al., 2008). IL-6 inhibits insulin-dependent signal transduction in liver. The experiment showed that the introduction of IL-6-neutralizing antibodies helped to reduce insulin resistance (Mas et al., 2009). In addition, enhanced synthesis of TNF-α, IL-6 and IL-8 is observed as a consequence of lipid peroxidation. Lipid peroxidation leads to hepatocyte necrosis and the development of inflammatory cell infiltration (Gaschler & Stockwell, 2017). Reactive oxygen species, necrosis of hepatocytes, TNF-α, IL-6 and IL-8 are activators of stellate cells, the stimulation of which is accompanied by excess production of extracellular matrix remodeling with the development of fibrosis/cirrhosis (Munsterman et al., 2018). Elevated levels of TNF-α and IL-6 are considered as markers of endotoxemia in NASH (Buechler & Bauer, 2012). Hyperproduction of TNF-α causes hyperproduction of IL-6 and further enhancement of insulin resistance (Bahceci et al., 2007).

IL-8, a family member of the chemokine, has a role in induction and amplification of inflammatory processes (Harada et al., 1994). Increased plasma IL 8 levels were detected in NASH patients (Bahcecioglu et al., 2005; Torer et al., 2007). Therefore, it may have a crucial role in NASH disease in which inflammation is a substantial pathophysiological feature. The (-251 A/T) polymorphism in IL 8 gene's promoter region is the only one influencing gene expression (Vairaktaris et al., 2007).

Aim

The current study's aim was to examine the serum levels of IL-6 and IL-8 and their associative relationships with anthropometric parameters and metabolic profiles in patients with type 2 diabetes, depending on the presence of NAFLD.

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Materials and methods

This cross-sectional study involved 375 patients aged 40-80 years from the Kyiv City Endocrinology Center who had type 2 diabetes. The following inclusion criteria are age over 18 years, the combination of T2D with NAFLD, or T2D without it. NAFLD diagnosis was concluded according to the recommendations of the American Gastroenterology Association (AGA) and American Association for the Study of Liver Disease (AASLD) on the basis of next: clinical examination, laboratory values of lipid and carbohydrate metabolism, liver enzyme activities (ALT, AST), ALT/AST ratio, and ultrasonography (US) examination (Chalasani et al., 2012). Exclusion criteria included chronic viral hepatitis (associated with HBV, HCV, HDV infection), idiopathic hemochromatosis, Wilson's disease, drug-induced liver illness, genetic failure of antitrypsin-1 and abuse of excessive amounts of alcohol (>210 grams of alcohol per week in men and >140 grams of alcohol per week in women over two years).

The ethics committee of Kyiv City Clinical Endocrinology Center approved the study.

All patients were divided according to the transaminases activity, in particular, the first group consist of 98 T2D patients who don't have NAFLD, group 2A – 150 patients with T2D and NAFLD with normal transaminases, group 2B – 127 patients with T2D and NAFLD with elevated transaminases activity.

In order to identify predictors of rapid progression of liver fibrosis in patients with T2D, a sub-analysis was conducted, which included 82 patients from group 2. The rate of fibrosis progression (RFP) in patients with T2D was calculated using the modified T. Poynard formula (the stage of liver fibrosis on the combined scale of FIB-4 and NAFLD score was divided by the duration of diabetes, measured in units per year (units/year). The median RFP in patients with T2D was 0.167 (0.05-0.5) units/year, respectively, patients were divided into two subgroups:

– with rapid progression of liver fibrosis (RFP> 0.167 units / year), n = 38;
– with slow progression of liver fibrosis (RFP≤0.167 units / year), n = 44.

Serum samples were taken from patients on an empty stomach who signed an informed consent. The biomaterial was immediately frozen at −80° C.

For each patient, relevant clinical characteristics and population data were collected. Anthropometric data, including height and weight, were measured to the nearest 0.5 cm and 100 g in accordance with. Body mass index (BMI) calculated the ratio of body weight in kilograms to height squared by a participant in meters.

To assess the functional state of the liver were studied total protein, bilirubin, ALT and AST activity, calculated the ratio of AST/ALT. ALT and AST activity were determined by UV kinetic method, total bilirubin and total protein levels by colorimetric method (ERBA Lachema, Czech Republic).

The diagnosis of fatty liver was based on the results of abdominal ultrasonography, which was done by trained technicians with Ultima PA (Radmir Co., Kharkiv, Ukraine). Of 4 known criteria (hepatorenal echo contrast, liver brightness, deep attenuation, and vascular blurring) (Hamaguchi et al., 2005), the participants had to have hepatorenal contrast and liver brightness to be diagnosed with NAFLD.

Also for confirmation of NAFLD diagnosis especially in case of US negative or contradictory data we used computer-assisted quantitative US techniques assessment. In these cases we used software programs to analyze US echo attenuation or calculate hepato-renal index which defined as the ratio of the echo intensities of the liver and renal cortex. These parameters have demonstrated higher sensitivities (> 90%) and specificity ((> 90%)) for mild steatosis detection (≥ 5%) as compared to routine B-mode US (Webb et al., 2009).

Fasting serum IL-6 and IL-8 concentrations were measured from plasma samples stored at −20°C using a commercial "peptide enzyme immunoassay" kit ("Protein Contour" (Russia).

Statistical analysis.

The SPSS statistical package, version 20.0 (SPSS, Inc., Chicago, Illinois), was used for all statistical analyses, and a *P* value less than 0.05 was considered statistically significant. All continuous values were expressed as mean ± SD, and categorical variables were presented as %. Data distribution was analyzed using the Kolmogorov-Smirnov normality test. Continuous

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variables with parametric distribution were then analyzed by performing an Analysis of Variance (ANOVA), and if the results were significant, a Bonferroni Post Hoc test was used. Data with non-parametric distribution was analyzed using the Kruskall-Wallis test. For comparisons of categorical variables, we executed the $\chi 2$ test.

Univariate and multivariate logistic regression analyses were performed to identify the risk factors of NAFLD. The odds ratios are given with 95% confidence intervals. Variables statistically significant in univariate analysis were included in the multivariate logistic regression analysis. The backward stepwise selection was used at a stringency level of $p<0.10$ to determine the independent risk factors of NAFLD. A $p<0.05$ probability level was considered as statistically significant.

Results and discussion

All patients were divided into the following groups: group 1 – patients with T2D (n = 98, 47 men (47.9%), 51 women (52.04%), aged 42 to 76 years, mean age – 55.1 ± 0.9; 95% CI 53.4-56.8); group 2 – patients with T2D and NAFLD (n = 277; men – 130 (46.9%), women – 147 (53.07%), aged 33 to 76 years, mean age – 56.9 ± 0.6 (95% CI 55.7-58.08).

To date, the role of inflammatory processes in the development of MS – a syndrome that is a major component of both T2D and NAFLD, is well known. Scientists believe that inflammatory mechanisms contribute to its progression. In 2016, a study in mice that were on a high-fat diet showed that blocking the IL-6 receptor decreased the accumulation of macrophages in adipose tissue. After activation and incorporation into tissues, macrophages cause inflammation through their own secreted mediators, which contribute to the development of adverse cardiovascular events and increase insulin resistance (Kraakman et al., 2015). IL-6 is secreted by M1 macrophages, which increases the level of CRP in MS (Ridker et al., 2004). In addition, IL-6 is associated with increased insulin resistance in adipocytes and hepatocytes (Pahwa, Adams-Huet & Jialal, 2017).

To prove the relationship between the indicators characterizing the pro-inflammatory profile of a patient with T2D and the occurrence of NAFLD, a simple logistic regression was performed first, and then a step-by-step multiple logistic regression analysis, which identified a reliable relationship between NAFLD and medical and demographic indicators, the state of carbohydrate and lipid metabolism.

Thus, we assume that IL-6 makes a significant contribution to the development of not only MS, but also NAFLD in patients with type 2 diabetes. Therefore, we analyzed the associations between the level of IL-6 and the main risk factors considerably associated with the development of NAFLD in patients with T2D. The study showed that the level of IL-6 in patients with T2D was significantly lower than in group 2A patients (10.38 ± 3.53 pg / ml vs. 16.16 ± 13.08 pg / ml; $p<0.001$) and group 2B (10.38 ± 3.53 pg / ml vs. 15.95 ± 6.37; $p<0.001$). Moreover, in univariate regression analysis IL-6 levels were significantly associated with age, T2D duration and severe form, as well with BMI, ALT, AST, and total bilirubin (table 1).

Table 1. Associations between IL-6 and components of the metabolic syndrome

Risk factors	Coef.	95% CI	p	_cons	95% CI	p
Age (years)	-0,004	-0,0069-0,0011	0,007	2,89	2,73-3,06	0,000
Female, (yes, no)	0,0228	-0,029-0,085	0,343	2,65	2,61-2,69	0,000
Smoking, (yes, no)	0,023	-0,035-0,082	0,431	2,65	2,62-2,69	0,000
T2D duration (years)	0,012	0,006-0,017	0,000	2,56	2,51-2,62	0,000
Severe T2D, (yes, no)	0,216	0,16-0,27	0,000	2,57	2,53-2,61	0,000
BMI (kg/m2)	0,032	0,026-0,037	0,000	1,59	1,41-1,78	0,000
ALT, IU/L	0,005	0,004-0,005	0,000	2,44	2,35-2,49	0,000
AST, IU/L	0,0055	0,0045-0,006	0,000	2,46	2,41-2,51	0,000
Total bilirubin, umol/l	0,023	0,016-0,028	0,000	2,24	2,13-2,36	0,000

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It was quite logical to identify reliable associations between the increase in IL-6 and the development of NAFLD. According to the results of univariate regression the odds ratio for development of NAFLD in patients with T2D is 1.14 (95% CI 1.09-1.21). However, in the multiple logistic regression analysis after correction for a number of factors, in which a reliable connection was obtained in a simple logistic regression analysis, we did not obtain significant association between IL-6 and NAFLD. From the other hand the serum IL-6 significantly associated with obesity parameters, as well as with elevated transaminases (table 2).

IL-8 is a crucial mediator associated with inflammation, where it performs an essential function in neutrophil recruitment and degranulation.

Table 2. Associations between NAFLD and IL-6 levels in patients with T2D in multiple logistic regression analysis

Risk factors	Odds Ratio	95% CI	p
IL -6, pg/ml	0,96	0,86-1,07	0,494
BMI (kg/m^2)	2,78	1,95-3,96	<0,001
ALT, IU/L	1,19	1,02-1,41	0,027
AST, IU/L	1,41	1,18-1,67	<0,001
Severe T2D, (yes, no)	12,87	2,77-59,59	0,001

The secretion of IL-8 is increased by oxidative stress, which causes recruitment of inflammatory cells and induces a further increase in oxidative stress mediators (Vlahopoulos et al., 1999). IL-8 also increases the expression of its own mRNA in adipocytes, which leads to persistent inflammation and infiltration of macrophages (Barchetta et al., 2019). This is confirmed by the work of I. Jialal, which showed a higher level of IL-8 in people with MS compared with control groups (Jialal et al., 2012). IL-8 synthesis and neutrophil infiltration increase in a high glucose environment due to elevated levels of active oxygen species and contribute to impaired wound healing in diabetic skin (Lan et al., 2013). Therefore, understanding such dysfunctions may be the basis for developing new therapeutic approaches in the management of NAFLD in patients with T2D.

We found significant relationship between IL-8 and a number of factors that characterize MS, including indirect with age and positive relationship with female, smoking status, duration and severity of T2D, BMI and a number of laboratory parameters such as ALT and AST activity (table 3).

Other studies have also shown an association between IL-8 and obesity (Sharabiani et al., 2011), but not in patients with type 2 diabetes. We found a relationship between the level of IL-8 and the development of NAFLD in simple regression logistic analysis – OR 1.12 (95% CI 1.06-1.17, $p > 0.001$). However, in multiple logistic

Table 3. Associations between IL-8 and components of the metabolic syndrome

Risk factors	Coef.	95% CI	p	_cons	95% CI	p
Age (years)	-0,003	-0,005-0,001	0,003	3,52	3,41-3,64	<0,001
Female, (yes, no)	0,070	0,031-0,109	<0,001	3,33	3,29-3,35	<0,001
Smoking, (yes, no)	0,078	0,038-0,117	<0,001	3,33	3,30-3,36	<0,001
T2D duration (years)	0,005	0,001-0,008	0,002	3,32	3,29-3,35	<0,001
Severe T2D, (yes, no)	0,138	0,098-0,177	<0,001	3,30	3,27-3,32	<0,001
BMI (kg/m^2)	0,026	0,022-0,029	<0,001	2,49	2,36-2,62	<0,001
ALT, IU/L	0,0032	0,0027-0,0036	<0,001	3,21	3,18-3,24	<0,001
AST, IU/L	0,004	0,0037-0,0049	<0,001	3,20	3,17-3,23	<0,001
Total bilirubin, umol/l	0,006	0,002-0,010	0,003	3,25	3,17-3,32	<0,001

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regression analysis, there were no significant associations between the occurrence of NAFLD and IL-8 levels. At the same time, the level of IL-8 was significantly associated with BMI, ALT, AST and the severity of T2D (table 4).

Table 4. Associations between NAFLD and IL-6 levels in patients with T2D in multiple logistic regression analysis

Risk factors	Odds Ratio	95% CI	p
IL -8, pg/ml	0,98	0,90-1,08	0,797
BMI (kg/m^2)	2,54	1,84-3,50	<0,001
ALT, IU/L	1,22	1,04-1,44	0,014
AST, IU/L	1,3	1,11-1,52	0,001
Severe T2D, (yes, no)	0,86	0,74-0,99	0,044

In sub-analysis the level of pro-inflammatory cytokine IL-8 in patients with RFP, the median value of its content was slightly higher than in patients with low RFP, but this difference was not statistically significant.

A study of anti-inflammatory interleukins in patients with diabetes showed that the median value of IL-6 was significantly lower in patients with rapid RFP than in patients with low RFP (9.8 vs. 13.8 pg / ml, p = 0.028). Therefore, higher level of IL-6 significantly reduces the chances of a patient with T2D to have a RFP (OR 0.94; p = 0.058) (table 5). Thus, we found a significant effect on the rapid RFP in patients with T2D of pro-inflammatory IL-8 and decreased levels of anti-inflammatory cytokine IL-6, indicating the role of prolonged inflammation in this condition. Thus, a number of authors testify that liver fibrosis is the result of a long process of wound healing (Schuppan & Pinzani, 2012; Trautwein, Friedman, & Pinzani, 2015). In animal experiments, it has been shown that the progression of NASH to fibrosis occurs in the case of recurrent attacks of inflammation, alternating with anti-inflammatory, reparative immune response (Teufel et al., 2016). This is especially true with changes in the environment and contributing to the development of fibrosis lifestyle (Vilar-Gomez et al., 2015).

Conclusion

We found significant relationships between the level of studied interleukins and the components of the metabolic syndrome. Both IL-6 and Il-8 levels are significantly associated with gender, duration and severity of T2D, BMI, ALT, AST and total bilirubin level in a simple logistic regression analysis. However, step-by-step multiple logistic regression analysis revealed no reliable link between both cytokines and NAFLD development. From the other hand elevated IL-8 and decreased IL-6 had a significant effect on the fibrosis progression in patients with NAFLD associated with T2D.

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Conflict of interests

The authors report no potential conflict of interest in any form; the paper was not, and it will not be the subject of commercial interest or reward.

Consent to publication

All authors have read and approved the final version of the manuscript. All authors have agreed to publish this manuscript.

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Table 5. Associations between rapid RFP and individual cytokines in patients with T2D in simple logistic regression analysis

Interleukins	Me (Q_1-Q_3)		P	OR, (95% CI)	p
	Low RFP (n = 44)	Rapid RFP (n = 38)			
IL-8, pg/ml	32,4 (24,4-41,9)	35,05 (25,5-46,6)	0,3991	1,011 (0,99-1,034)	0,310
IL-6, pg/ml	13,8 (8,8-20,75)	9,8 (8,1-13,0)	0,028	0,94 (0,88-1,00)	0,058

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A – Research concept and design, B – Collection and/or assembly of data, C – Data analysis and interpretation, D – Writing the article, E – Critical revision of the article, F – Final approval of the article.

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Рівень ІЛ-6 та ІЛ-8 та їх асоціативний зв'язок з неалкогольною жировою хворобою печінки у хворих на цукровий діабет 2 типу

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Анотація: *неалкогольна жирова хвороба печінки (НАЖХП) характеризується накопиченням ліпідів у гепатоцитах понад 5% маси печінки за відсутності надмірного споживання алкоголю та вторинних причин захворювань органу. Зусилля багатьох вчених у всьому світі зосереджені на покращенні розуміння патогенетичних процесів і тригерів прогресування НАЖХП, з акцентом на одночасному вивченні кількох патофізіологічних шляхів для виявлення порушень у всьому спектрі захворювання. Метою роботи було дослідити рівні інтерлейкіну (ІЛ)-6 та ІЛ-8 в сироватці крові та їх асоціативні зв'язки з антропометричними параметрами та метаболічним профілем у пацієнтів із цукровим діабетом 2-го типу (ЦД2) в залежності від наявності НАЖХП. У дослідження було включено 375 пацієнтів із ЦД2 у віці 40–80 років. Усіх пацієнтів розділили на 3 групи. До контрольної групи увійшли 98 хворих на ЦД2 без НАЖХП. До основної групи увійшли хворі на ЦД2 з НАЖХП, які були поділені на 2 підгрупи залежно від активності трансаміназ: з нормальною активністю (група 2А, n = 150) та з підвищеною (група 2В, n = 127). З метою виявлення предикторів швидкого прогресування фіброзу печінки у хворих на ЦД2 було проведено субаналіз, до якого увійшли 82 пацієнти. Виявлено статистично значущі зв'язки між рівнем досліджених ІЛ та компонентами метаболічного синдрому. За допомогою простого логістичного регресійного аналізу встановлено, що рівні ІЛ-6 і ІЛ-8 значною мірою пов'язані зі статтю, тривалістю та тяжкістю ЦД2, індексом маси тіла, активністю аланінамінотрансферази (АЛТ) і аспартатамінотрансферази (АСТ) та рівнем загального білірубіну. Однак покроковий множинний логістичний регресійний аналіз не виявив значущого зв'язку між обома цитокінами та розвитком НАЖХП. З іншого боку, підвищений IL-8 і знижений IL-6 мали значний вплив на прогресування фіброзу в пацієнтів з НАЖХП, пов'язаною з ЦД2. Наше дослідження продемонструвало значний зв'язок між рівнем IL-6 і IL-8 та компонентами метаболічного синдрому, такими як ожиріння або активність трансаміназ, але не з самою НАЖХП.*

Ключові слова: цукровий діабет 2 типу; неалкогольна жирова хвороба печінки, інтерлейкін-6, інтерлейкін-8, метаболічний синдром, інсулінорезистентність, ожиріння.