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THE ROLE OF LIPID METABOLISM IN THE DEVELOPMENT OF ENDOTHELIAL DYSFUNCTION IN DIABETIC NEPHROPATHY

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The purpose of the study was to study the relationship between lipid metabolism and flow-mediated dilation and endothelium-independent vascular dilation in diabetic nephropathy patients. The study included 120 patients with chronic kidney disease against the background of diabetic nephropathy. They were divided into 4 groups according to the stages of disease. The level of flow-mediated dilation in the brachial artery was determined by the hyperemic test and the level of endothelium-independent vascular dilation by the nitroglycerin test. The lipid spectrum was assessed by the level of total cholesterol, triglycerides, high-density lipoproteins, low-density lipoproteins in blood serum, as well as by calculating the atherogenic coefficient. In the 1st group, a moderate inverse relationship was determined between flow-mediated dilation and total cholesterol, triglycerides, atherogenic coefficient (respectively, r=–0.503, p<0.05; r=–0.513, p<0 0.05; r=–0.531, p<0.05). At subsequent stages of chronic kidney disease, the correlation in the groups was of the same nature (0.726, p<0.01). Thus, the results obtained indicate the effect of changes in the blood lipid spectrum on the degree of flow-mediated dilation and absence of influence on endothelium-independent vascular dilation.

Key words: diabetic nephropathy, flow-mediated dilation, nitroglycerine-induced vasodilation, lipid metabolism

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РОЛЬ ЛІПІДНОГО ОБМІНУ У РОЗВИТКУ ЕНДОТЕЛІАЛЬНОЇ ДИСФУНКЦІЇ ПРИ ДІАБЕТИЧНІЙ НЕФРОПАТІЇ

Метою дослідження було вивчення взаємозв'язку між ліпідним обміном та потік-опосередкованою дилатацією, а також ендотелійнезалежною судинною дилатацією у хворих на діабетичну нефропатію. Було обстежено 120 хворих з хронічною хворобою нирок, що розвинулася на фоні діабетичної нефропатії, розділених на 4 групи, залежно від стадії. Визначали рівень потік-опосередкованої дилатації плечової артерії за допомогою гіперемічної проби та рівень ендотелійнезалежної судинної дилатації за допомогою нітрогліцеринової проби. Ліпідний спектр оцінювали за рівнем загального холестерину, тригліцеридів, ліпопротеїдів високої щільності, ліпопротеїдів низької щільності у сироватці крові, а також шляхом розрахунку коефіцієнта атерогенності. У 1-й групі визначалася помірна зворотна залежність між потік-опосередкованою дилатацією та загальним холестерином, тригліцеридами, коефіцієнтом атерогенності (відповідно r=-0,503, p<0,05; r=-0,513, p<0,05); r =-0,531, p <0,05). При наступних стадіях хронічної хвороби нирок співвідношення групи було такого ж характеру (0,726, p<0,01). Таким чином, отримані результати свідчать про вплив змін ліпідного спектру крові на ступінь потік-опосередкованої дилатації, але відсутність впливу на ендотелій-незалежну судинну дилатацію.

Ключові слова: діабетична нефропатія, потік-опосередкована дилатація, нітрогліцерин-індукована вазодилатація, ліпідний обмін.

Diabetes mellitus (DM) is at the forefront of the etiological causes of CKD [2, 5]. Currently, the spread of DM in the world has taken on the character of a non-communicable epidemic. According to the World Health Organization (WHO), the number of patients with type 2 DM by 2025 may reach 380 million [13]. Recent studies have revealed that endothelial dysfunction (ED) is the cause of the rapid development of macro- and microangiopathies in patients with DM [1, 7]. In diabetic patients, ED is considered the earliest sign of vascular damage and can be detected in the primary stages of the disease, even before atherosclerotic plaques are detected [2]. Thus, ED, being an early manifestation of the lesion, is considered a prognostically important marker.

ED also plays a significant role in the last stages of atherosclerotic lesions. Thus, a violation of the endothelial reaction and an increase in adhesion leads to spasm, the development of plaques and, ultimately, a violation of the integrity of the endothelial surface [6]. It was revealed that ED is a trigger pathogenetic mechanism in the development of nephropathy in patients with DM [9]. For this reason, endothelial dysfunction in diabetic patients is under the consistent and close supervision of researchers. [12, 13]. Impaired endothelium-dependent vasodilation (EDVD) is also involved in the progression of CKD. An increase in the response to vasoconstrictor agents leads to an increase in the reactivity of micro vessels, which, in turn, disrupts the synthesis of vasodilatory factors [4]. To prevent the progression of CKD, early diagnosis of ED is extremely important. Another method for assessing the functional state of the endothelium is the study of endothelial-damaging factors, the plasma level of which correlates with ED.

The purpose of the study was to establish the relationship between lipid metabolism and flow-mediated dilation and endothelium-independent vasodilation in diabetic nephropathy.

Materials and methods. During the study, 120 patients aged 20–60 years (mean 45.5±1.02 years) with CKD who received inpatient treatment were examined. Of these, 58 patients were female (48 %), and 62 male patients (52 %). In all patients, the cause of CKD was diabetic nephropathy. All patients were divided into 4 groups according to CKD stages. The 1st group included 30 patients with an average age of

50.7±1.45 years, with a disease duration of 7.82±0.76 years, with a glomerular filtration rate (GFR) of 98.5±1.37 ml/min/1.73m^2, group 2, respectively, consisted of 29 patients aged 50.4±1.18 years, with a disease duration of 9.33±0.84 years, with a GFR of 67.7±2.25 ml/min/1.73m^2, the 3rd group included 30 patients (mean age–53.4±1.04 years) with a disease duration of 10.00±0.58 years, with a GFR of 38.9±1.60 ml/min /1.73m^2, in the 4th group – 29 patients (mean age–55.1±0.99 years), respectively, with the duration of the disease 13.69±1.26 years and GFR 26.45±0.85 ml/min /1.73m^2. 30 healthy individuals (mean age 41.2±1.09 years) constituted the control group.

All patients underwent clinical and laboratory-instrumental studies. GFR was calculated using the CKD EPI calculation method. In all 4 groups, the level of flow-mediated dilation (FMD) in the brachial artery was determined by the hyperemic test and the level of Nitroglycerine-induced vasodilation (NID). The lipid spectrum was assessed by the level of total cholesterol (TC), triglycerides (TG), high density lipoproteins (HDL), low density lipoproteins (LDL) in blood serum, as well as by calculating the atherogenic coefficient (AC). The level of TC, TG, HDL was determined by the enzymatic method. The principle of the method is that cholesterol is oxidized by cholesterol oxidase, releasing hydrogen peroxide, which, in the presence of peroxidase, converts p-aminoatipyrine into a colored compound. The color intensity is proportional to the concentration of cholesterol levels.

To characterize groups of homogeneous units, the arithmetic mean (M), standard error (m) and range of change were determined. To study the qualitative indicators, the absolute number of groups and their percentage were determined. To compare quantitative indicators, the nonparametric Mann-Whitney test was used, which evaluates the difference between the indicators. The statistical difference $p<0.05$ was assessed as significant. For a statistical study of the cause-and-effect relationship, a non-parametric method was used - the Spearman rank correlation coefficient. This method determines the measure of linear relationship between random variables. When using rank correlation, if the correlation coefficient between the indicators is 0.3 or less, then the correlation is considered weak, if 0.4-0.7 is medium, 0.7 and above is high.

Results of the study and their discussion. At the 1st stage of CKD, the decrease in the reaction of the endothelium averaged 9.78±0.16 %. At the same time, in 76.47 % of patients, FMD was less than 10 %. As CKD progressed, that is, as kidney function declined, there was also a decrease in FMD below 10 %. (Table 1).

Table 1

Level of FMD and NID depending on the stage of CKD in diabetic nephropathy patients

	DN (n=120)				
	Control group (healthy individuals) n=30	I group n=30	II group n=29	III group n=30	IV group n=31
FMD (%)	14.0±0.06 (13.5–14.7)	9.78±0.16* (9.2–11.8)	9.30±0.19 (8.2–11.4) $p_1>0.05$	8.25±0.28* (7.2–10.8) $p_1<0.001$ $p_2<0.01$	7.46±0.24* (6.0–9.0) $p_1<0.001$ $p_2<0.001$ $p_3<0.05$
NID	14.9±0.07 (14.2–15.5)	12.35±0.11* (11.8–13.4)	11.2±0.10* (10.9–12.1) $p_1<0.001$	9.68±0.06* (9.3–10.2) $p_1<0.001$ $p_2<0.001$	8.54±0.08* (7.9–9.2) $p_1<0.001$ $p_2<0.001$ $p_3<0.001$

Note: *–indicator of statistical significance between patient and healthy groups ($p<0.05$). p1, p2, p3 - statistically significant difference compared to the indicators of groups 1, 2 and 3, respectively.

Thus, at the 2nd stage of CKD, FMD averaged 9.30±0.19 % but did not differ in statistical significance from the control group ($p>0.05$). If there was no statistically significant difference between the 1st and 2nd groups, then in the 3rd and 4th groups, the FMD was 8.25±0.28 % and 7.46±0.24 %, respectively, and, in these groups, both among themselves and in comparison, with the healthy group, there was a statistically significant difference.

Even though in the 2nd and 3rd groups there were cases when FMD was below 10 %, in the 4th group in all patients FMD was <10 % (fig. 1).

So, in the 2nd in 93.33 %, in the 3rd in 81.25 % of cases there was a change of the FMD.

In the 1st group, NID, averaging 12.35±0.11 %, and in the 2nd group, respectively, 11.2±0.10 %, meant a normal reaction. The data obtained differed from the control group in statistical significance ($p<0.05$).

In DN patients, starting from the 3rd stage of CKD, NID was below 10 %, in the 4th group, a significant decrease in this indicator was noted. Thus, despite the fact that in the 3rd group the maximum NID was 10.2 %, its mean value was 9.68±0.06 %. In the 4th group, there was not a single patient with NID above 10% and the mean value was 8.54±0.08 %. The results obtained were statistically more significant than the control group ($p<0.05$).

At the 1st and 2nd stages of CKD in all patients, NID was more than 10 %. However, in the subsequent 3rd and 4th stages, the frequency of changes increased. So, if at the 3rd stage of CKD in the 3rd group in 2 patients (12.5 %) NID was >10 %, then in the 4th group in 31 patients (100 %), that is, in all NID was <10 % (fig. 2).

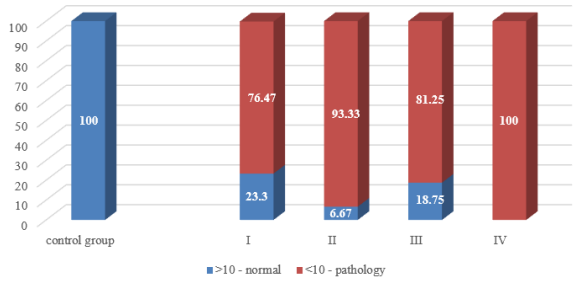

Fig. 1. Rate of change in FMD

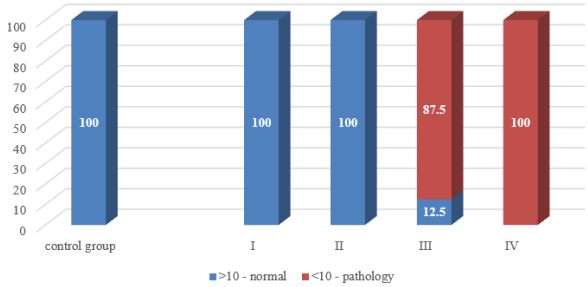

Fig. 2. Frequency of change in NID

To assess the dependence of vasodilation and lipid spectrum in patients with CKD, the presence and degree of dyslipoproteinemia were determined. In groups, depending on the stage of CKD, changes in the lipid spectrum were of a different nature and frequency (Table 2).

Table 2

Lipid spectrum indices in DN depending on the stage of CKD

Indices	Control group	DN n=120			
		I group n=30	II group n=29	III group n=30	IV group n=31
TC, mg/dl	165.2±4.06 (129.0–201.0)	254.1±4.55* (220.0–284.0)	282.7±3.05* (265.0–301.0) p_1<0.001	299.9±10.32* (254.0–398.0) p_1<0.01 p_2>0.05	388.0±21.34* (290.0–641.0) p_1<0.001 p_2<0.001 p_3<0.001
TG, mg/dl	105.5±5.62 (58.0–147.0)	121.6±8.18 (60.0–170.0)	143.7±8.57* (78.0–180.0) p_1>0.05	138.9±7.88* (90.0–195.0) p_1>0.05 p_2>0.05	167.9±10.08* (100.0–228.0) p_1<0.001 p_2>0.05 p_3<0.05
HDL, mg/dl	56.3±2.01 (42.0–80.0)	57.2±4.16 (28.0–77.0)	38.3±2.09* (21.0–52.0) p_1<0.001	37.9±1.58* (24.0–48.0) p_1<0.001 p_2>0.05	31.9±1.12* (24.0–39.0) p_1<0.001 p_2<0.05 p_3<0.01
LDL, mg/dl	67.5±3.97 (14.0–90.0)	72.0±3.72 (46.0–98.0)	131.6±8.77* (72.0–193.0) p_1<0.001	143.4±8.76* (74.0–199.0) p_1<0.001 p_2>0.05	166.1±10.51* (82.0–229.0) p_1<0.001 p_2<0.05 p_3>0.05
AC	2.04±0.13 (0.75–3.40)	3.98±0.48* (1.9–7.9)	6.75±0.51*# (4.2–11.6) p_1<0.001	7.15±0.46* (4.8–10.9) p_1<0.001 p_2>0.05	11.61±1.12* (7.7–25.7) p_1<0.001 p_2<0.001 p_3<0.001

Note: * – index of statistical significance between sick and healthy groups (p<0.05); # – the difference between the indicators of the respective groups is statistically significant p<0.05); p1, p2, p3 – statistically significant difference compared to indices in groups 1, 2 and 3, respectively.

As CKD progressed, there was a statistically significant difference from the control group in the level of total cholesterol and this index was significantly higher than the average values (p<0.05).

In the 2nd group, the concentration of total cholesterol differed in statistical significance from the 1st group (p<0.05). Despite the fact that this index in the 3rd and 4th groups did not differ statistically significantly, at the 4th stage, its concentration increased significantly and amounted to 290.0–641.0 mg/dl. In contrast, an increase in the level of TG concentration was noted at all stages of CKD, only in the 4th group the result obtained was statistically significantly different from other groups. At all stages of CKD, HDL and LDL levels changed. It is known that a decrease in HDL concentration is an independent risk factor for cardiovascular complications. In the 1st group, the average HDL concentration did not change. Despite this, in this group, the minimum HDL value was 28.0 mg/dl. However, in the subsequent stages of CKD, a significant decrease in this index was observed. So, in the 2nd group, its concentration was 38.3±2.09 mg/dl, in the 3rd group – 37.9±1.58 mg/dl, in the 4th group it was 31.9±1.12 mg/dL.

In groups 2–4, corresponding to the stages of CKD, there was an increase in the concentration of LDL. At this time, a statistically significant difference was revealed between the 1st and 2nd groups ($p<0.001$).

AC is an integral index and allows you to determine in advance the risk of atherosclerosis with high accuracy. However, in the 2nd and 4th groups, there was a statistically significant difference in the KA index between the group. Thus, in the 2nd group this index was 6.75±0.51, in the 4th group it was 11.61±1.12. There is significant increase in the risk of developing atherosclerosis in the 1st group compared to the control group. In group 3, dyslipidemia was detected as a statistical increase in total cholesterol and atherogenic lipoproteins. The revealed changes depended on GFR. In the course of the study, at various stages of CKD, along with the analysis of the results of the lipid spectrum in both groups, a study of its correlation with FMD and NID was also conducted. Already from the initial stage of CKD, a statistically significant correlation between the level of FMD and the lipid spectrum was determined. So, in the 1st group, a moderately average correlation was detected between EDVD and indicators of total cholesterol, TG and CA ($r=–0.503$, $p<0.05$; $r=–0.513$, $p<0.05$; $r=–0.531$, $p<0.05$ respectively). In subsequent stages of CKD, the correlation was of the same nature. In the 4th group, a high correlation was determined between EVD and CA ($r=–0.726$, $p<0.01$). The correlation between NID and the lipid spectrum was also studied, and the correlation between these indicators was practically not detected.

Various researchers have identified a prognostically significant role of a decrease in EDVD in the development of the atherosclerotic process, diseases of the cardiovascular system, and mortality [2, 6]. It is believed that lipid deposits in the glomerular capillaries reduce glomerular filtration. This, in turn, increases the intraglomerular pressure of intact nephrons, thus contributing to the development of glomerulosclerosis [6, 9]. It is believed that the greatest damage to the renal glomeruli occurs with an increase in the level of total cholesterol. So, in the conducted studies, for nephrotic hyperlipidemia, first of all, a significant increase in total cholesterol was characteristic [4, 8]. Along with an increase in the level of total cholesterol, proteinuria also increased and the number of sclerosed glomeruli increased. In clinical studies, it has been indicated that in any nephropathy, hyperlipidemia contributes to the progression of renal failure. Thus, the progression of renal failure depends on the level of total cholesterol, TG, LDL, HDL [1, 3]. In nephrotic syndrome, TG and LDL levels increase, HDL levels remain within the normal range, or slightly decrease [10].

Based on our results, we can conclude that there is a pattern between ED and kidney dysfunction. So, during the study, the correlation between functional biomarkers of the endothelium and functional indicators of the kidneys was studied. During the study, an association between ED and a decrease in glomerular filtration rate was noted, which is also confirmed by many studies. Various researchers have identified a prognostically significant role of a decrease in EDVD in the development of the atherosclerotic process, diseases of the cardiovascular system, and mortality [4, 11]. For our part, it was found that in patients with CKD, ED and atherogenesis, being a single process, is important in the progression of CKD, and, accordingly, this can significantly help in the development of diagnostic criteria. As CKD progresses, endothelial activity changes and endothelium-dependent vasodilation decreases.

Conclusions

1. In the 1st group, a moderate inverse relationship was determined between flow-mediated dilation and total cholesterol, triglycerides, atherogenic coefficient (respectively, $r=–0.503$, $p<0.05$; $r=–0.513$, $p<0$ 0.05; $r=–0.531$, $p<0.05$). At subsequent stages of chronic kidney disease, the correlation in the groups was of the same nature (0.726, $p<0.01$).

2. In groups 2–4, corresponding to the stages of CKD, there was an increase in the concentration of LDL. At this time, a statistically significant difference was revealed between the 1st and 2nd groups ($p<0.001$).

3. The correlation between NID and the lipid spectrum was practically not detected. Thus, the results obtained indicate the effect of changes in the blood lipid spectrum on the degree of FMD. In contrast, a high correlation between NID and lipid spectrum was not characteristic. Larger scale studies are required to obtain more reliable results.

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GENDER DIFFERENCES IN COVID-19 VACCINATION IN UKRAINE

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The COVID-19 pandemic is among the greatest challenges for the worldwide. Vaccine development is an effective weapon against pandemic development. But there is a paucity of data of COVID-19 vaccine data by sex/gender in Ukraine. The purpose of the study was to assess diversity in COVID-19 vaccination among gender groups of Ukrainian population. A retrospective-archive study was conducted in Ukraine from 24 February 2021 to 16 January 2022. The obtained data showed in trends gender differences in COVID-19 vaccination status. Women preferred vaccination with Pfizer/Biontech and AstraZeneca vaccines more often than men. Significantly higher level of weekly cases among persons who received two doses than one dose of Pfizer/BioNTech vaccine with as among males ($p<0.05$), as females ($p<0.05$). These findings support idea that a gendered lens should also be applied when designing COVID-19 vaccination campaign that can help to maximize benefits and minimize adverse events.

Key words: vaccine, SARS-CoV-2, sex, Ukraine

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ГЕНДЕРНІ ВІДМІННОСТІ У ВАКЦИНАЦІЇ ВІД COVID-19 В УКРАЇНІ

Пандемія COVID-19 є одним із найбільших викликів для всього світу. Розробка вакцин є ефективним засобом боротьби проти розвитку пандемії. Проте, даних про COVID-19 вакцинацію за статтю/гендером в Україні мало. Метою дослідження було оцінити різноманітність вакцинації проти COVID-19 серед гендерних груп українського населення. Ретроспективно-архівне дослідження проводилося в Україні з 24 лютого 2021 року по 16 січня 2022 року. Встановлено гендерні відмінності в трендах вакцинації проти COVID-19. Жінки віддавали перевагу щепленню вакцинами Pfizer/Biontech та AstraZeneca частіше, ніж чоловіки. Відмічено вірогідно вищу кількість тижневих випадків вакцинації двома дозами вакцини Pfizer/BioNTech, ніж однією дозою, як серед чоловіків ($p<0.05$), так і серед жінок ($p<0.05$). Отримані дані дозволяють зробити висновки про необхідність врахування гендерної відмінності при плануванні кампанії вакцинації проти COVID-19, що сприятиме максимізації переваг та мінімізації побічних ефектів.

Ключові слова: вакцина, SARS-CoV-2, стать, Україна

The study is a fragment of the research projects: "The study of the role of exogenous and endogenous factors in the regulation of the body's protective and adaptive systems", state registration No. 0118U004460.

The COVID-19 pandemic is among the greatest challenges for the worldwide. In Ukraine more than 5.4 million people have already been infected with SARS-CoV-2 and with 110 920 deaths [3,10]. COVID-19 vaccine development is an effective weapon against pandemic [12]. Five types of COVID-19 vaccines (AstraZeneca (Covishield, SKBio), Coronavac/Sinovac Biotech, Comirnaty/Pfizer-BioNTech.) have been approved and vaccination rates accelerated as of February 24, 2021. It was estimated that 50–70% rates of vaccination are needs to receive for development herd immunity and protection from a severe increase of infections SARS-CoV-2. But there is a paucity of data of COVID-19 vaccine data by sex/gender in Ukraine. Therefore, analysis of COVID-19 vaccination trends with a gender-sensitive way can help to assist in building public confidence and promote high vaccine coverage.