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PROGRESSION OF DIABETIC RETINOPATHY AND BLOOD FIBRINOGEN IN PATIENTS WITH TYPE 2 DIABETES

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ПРОГРЕССИРОВАНИЕ ДИАБЕТИЧЕСКОЙ РЕТИНОПАТИИ И ФИБРИНОГЕН КРОВИ У ПАЦИЕНТОВ С САХАРНЫМ ДИАБЕТОМ 2 ТИПА

Summary. Objective - to study the effect of blood fibrinogen in patients with type 2 diabetes mellitus on the progression of diabetic retinopathy. **Material and methods.** The research was carried out on 64 patients (95 eyes) with T2D, MS and DRP (males and females, average age 61.55±2.37 years old, average length of diabetes 11.23±2.11 years, average level of HbA1C 9.89±0.78%, average BMI 34.55±3.75 kg/m2), who were divided into 3 groups depending on the stage of DRP. Procoagulant potential was estimated by fibrinogen concentration in blood serum. The ANOVA and regression analysis were used as statistical analysis. **Results.** A clinically

significant increase of the blood fibrinogen concentration is observed at the age of patients over 60 years (exceeding the permissible values by 31%), with a duration of diabetes more than 10 years (exceeding by 34%), at subcompensation of T2D (HbA1C less than 8%) (exceeding by 29%) – in the proliferative stage of DRP. **Conclusions.** With the progression of DRP from nonproliferative to proliferative stage on the background of MS a significant increase in blood fibrinogen concentration occurs (316.4±10.8 μg/dl, 95% CI 301.1-331.6 μg/dL – the 1-st stage vs 368.6±23.8 μg/dl, 95% CI 334.7-402.3 μg/dL – the 3-rd stage, p2<0.05). A reliable positive nonlinear association of the blood fibrinogen concentration with T2D duration (r=0.38, R2=14.4%, p=0.03) was revealed, especially during the first 10 years from the onset of the disease.

Резюме. Цель – изучить влияние фибриногена крови у больных сахарным диабетом 2 типа на прогрессирование диабетической ретинопатии. **Материал и методы.** Исследования проведены у 64 пациентов (95 глаз) с МС, СД 2 типа и ДРП (мужчины и женщины, средний возраст 61,55±2,37 года, средний стаж диабета 11,23±2,11 года, средний уровень гликированного гемоглобина (HbA1C) 9,89±0,78%, средний индекс массы тела 34,55±3,75 кг/м2), которых разделили на 3 группы в зависимости от стадии ДРП. Прокоагуляционный потенциал оценивали по показателям концентрации фибриногена сыворотки крови. Статистическую обработку проводили с помощью одно- и двухфакторного дисперсионного анализа и регрессионного анализа. **Результаты.** Клинически значимое повышение концентрации фибриногена в крови отмечается в возрасте пациентов более 60 лет (превышение допустимых значений на 31%), при длительности диабета более 10 лет (превышение на 34%), при субкомпенсации СД 2 типа (HbA1C менее 8%) (превышение на 29%) – на пролиферативной стадии ДРП. **Выводы.** При прогрессировании ДРП от непролиферативной к пролиферативной стадии на фоне МС происходит достоверное увеличение концентрации фибриногена в крови (316,4±10,8 мкг/дл, 95% ДИ 301,1-331,6 мкг/дл – 1 стадия vs 368,6±23,8 мкг/дл, 95% ДИ 334,7-402,3 мкг/дл – 3 стадия, p2 <0,05). Выявлена достоверная позитивная нелинейная ассоциация концентрации фибриногена в крови и длительности СД 2 типа (r=0,38; R2=14,4%; p=0,03), особенно на протяжении первых 10 лет от начала заболевания.

Key words: diabetic retinopathy, fibrinogen, type 2 diabetes, metabolic syndrome.

Ключевые слова: диабетическая ретинопатия, фибриноген, сахарный диабет 2 типа, метаболический синдром.

INTRODUCTION

Metabolic syndrome (MS) is traditionally characterized by dyslipidemia, high blood pressure, abdominal obesity, hyperglycemia and insulinresistance [5, 9]. However, it is presently considered that MS also is related to the levels of fibrinogen, urinary acid, C-reactive albumen, leptin, interleukins in blood, endothelial dysfunction and a diabetes mellitus type 2 [1].

It is shown that combination MS with such cluster as a hyperfibrinogenemia increases the risk of development micro- and macrovascular complications, including diabetic retinopathy (DDR) [8], which indicates the relevance of further studies of the relationship between the level of fibrinogen and the risk of development and progression of DRP in type 2 diabetes as a component of MS.

Aim of work - to study the effect of blood fibrinogen in patients with type 2 diabetes mellitus on the progression of diabetic retinopathy

MATERIALS AND METHODS

Studies were performed in 64 patients (95 eyes) with MS, type 2 diabetes and DRP (men and women, medium age 61.55 ± 2.37 years, average diabetes 11.23 ± 2.11 years, average glycated hemoglobin (HbA1C) 9.89 ± 0.78%, average BMI 34.55 ± 3.75 kg / m2), which were divided into 3 groups depending on the stage of the DRP. A control group consisted of 16 persons with surplus body weight or obesity without diabetes (men and women, middle age 61,23±5,46 year, middle BMI 32,99±4,81 kg/of m2). Work is executed in accordance with the requirements of Helsinki declaration of the World medical association (2008), by the orders of Ministry of health of Ukraine № 281 from 01.11.2000, № 355 from 25.09.2002, №1118 from 21.12.2012. The criteria of exception from research it was been: presence of endocrine and somatic diseases resulting in obesity, acute infectious diseases, DM of a 1 type, oncologic diseases, decompensation of comorbid pathology, mental disorders, intake antipsychotics and antidepressants, proteinuria, clinically meaningful maculopathy, damage of visual nerve, glaucoma and cataract [3].

In patients of the study and control groups, growth, a height, body weight, volume of waist and thighs were measured, body mass index (BMI) was calculated, systolic and diastolic blood pressure were recorded, serum concentrations of total cholesterol, high density lipoprotein (HDL), low density lipoprotein (LDL) and triglyceride (TG), as well as levels fasting glucose and HbA1C (in patients with type 2 diabetes) were determined.

MS was determined by the Working criteria of experts of the National institute of health to the USA (Adult Treatment Panel III, ATP III, 2001) confessed by World Health Organization [5, 6]. The concentration of glucose in plasma of blood was determined by a glucose oxidase method, and in capillary blood - by a enzymatic colorimetric method, concentration of HbA1C in blood - by the method of liquid ion exchange chromatography of high-pressure, concentration of TG, total cholesterol and his factions - by a spectrophotometry method.

Procoagulative potential was estimated on the indexes of concentration of fibrinogen of serum of blood, that was determined by a clotting method. Less

than 8% was chosen as the level of comparison of HbA1C taking into account the patient-oriented approach and life expectancy [2, 7]. All patients underwent a comprehensive ophthalmological examination using autorefractometry, visometry, tonometry, perimetry, biomicroscopy, fundus photography and fluorescence fundus angiography (as indicated). The diagnosis of DRP was made according to the order of the Ministry of Health of Ukraine dated 05.22.2009 No. 356 as amended by the order of the Ministry of Health of Ukraine dated 05.08.2009 No. 574, in which it is recommended to distinguish 3 main stages of DRP: non-proliferative, preproliferative and proliferative.

Statistical processing was performed using one- and two-way analysis of variance and regression analysis. The Fisher parametric test or the Kruskal-Wallis nonparametric test were used. The characteristics of the regression models were considered: r is the correlation coefficient, R2 is the coefficient of determination, p is the level of statistical significance of the models. Statistical characteristics are presented as arithmetic mean (M) and standard error (± m), 95% confidence interval (95% CI). Differences were considered statistically significant if $p < 0.05$. Statistical analysis of the data was carried out using the computer program "SPSS 9.0". Calculations and graphing of curves were carried out in the statistical computer package Statgraphics 3 for Windows.

RESULTS AND ITS DISCUSSION

Indicators of fibrinogen in the blood of patients with MS and type 2 diabetes at different stages of DRP are presented in table 1. As the results of the analysis of variance showed, the fibrinogen levels in the blood exceeded the upper level of acceptable values (less than 350 μg / dl) at the 3rd stage of the DRP both in average values (368.6 μg / dl) and in CI (402.3 μg / dl), and statistically significant differences were revealed when comparing the average fibrinogen values in patients at the 1st and 3rd stages of DRP ($p < 0.05$). There were no differences in this indicator between the main groups and the comparison group (obesity) with a tendency to increase the level of fibrinogen during the transition from the 1st stage to the 2nd and already a significant increase in its concentration at the 3rd stage of DRP.

Table 1

The average blood fibrinogen concentration depending on the stage of diabetic retinopathy (N; M + m; 95% CI)

Indicator	Statistical indicator	Obese people without type 2 diabetes	Patients with diabetic retinopathy		
			1st stage	2st stage	3st stage
Fibrinogen, mcg / dl	N M±m 95% CI	16 326,5±16,4 303,3–349,6	42 316,4±10,8 301,1–331,6	12 346,7±22,5 314,9–378,5	10 368,6±23,8 334,7–402,3 p2 <0,05

Note: n is the number of persons in groups; CI - confidence interval; p is the level of statistical significance (F-test) in comparison with the specified group.

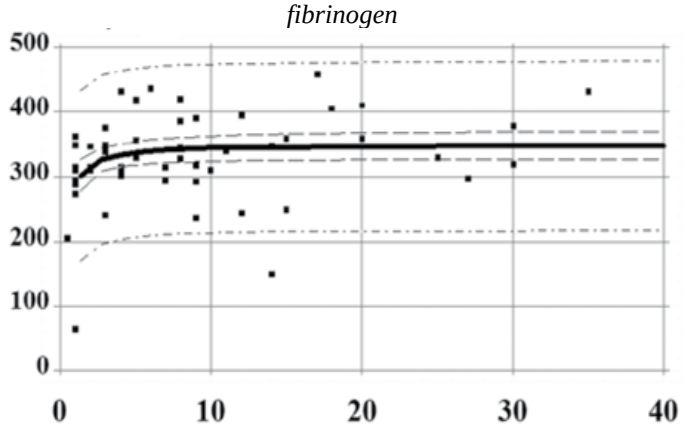

Fig. The dependence of the concentration of fibrinogen in the blood on the duration of type 2 diabetes in patients with diabetic retinopathy on the background of metabolic syndrome.

Fibrinogen levels in the blood of patients with MS and Type 2 diabetes, taking into account the age of patients, duration diabetes from the time of diagnosis and level HbA1C are presented in table 2.

Table 2

The average statistical concentration of fibrinogen in the blood at different stages diabetic retinopathy depending on the factors of its progression

Comparison groups	Stat. indicators	Diabetic retinopathy		
		1st stage (n = 25)	2nd stage (n = 12)	3rd stage (n = 10)
Patient age ≤60 years	M ± m 95% CI	310,3±13,8 282,4–338,1	367,3±39,2 288,6–446,1	347,1±33,9 278,9–415,3
Patient age> 60 years	M ± m 95% CI	326,1±17,5 290,8–361,3	336,4±27,7 280,7–392,1	390,0±33,9 321,8–458,2 p <0,05*
Duration of diabetes from the moment of registration ≤10 years	M ± m 95% CI	318,1±12,2 293,5–342,6	316,9±33,8 248,9–384,8	354,7±30,2 293,9–415,4
Duration of diabetes from registration> 10 years	M ± m 95% CI	310,6±22,3 265,9–355,4	370,6±30,2 309,8–431,4	391,6±39,0 313,1–470,1 p<0,1**
Diabetes subcompensation (HbA1C ≤8%)	M ± m 95% CI	289,1±19,1 250,7–327,5	312,2±46,8 218,0–406,3	373,6±38,2 296,8–450,5
Diabetes decompensation (HbA1C> 8%)	M ± m 95% CI	331,7±12,9 305,6–357,8	356,6±25,0 306,3–406,9	365,5±29,6 305,9–425,0

Note: n is the number of persons in groups; CI - confidence interval, * - significance of differences in compared with the 1st stage at the age of 60 years, ** - significance of differences compared with the 1st stage with diabetes lasting up to 10 years, *** - significance of differences compared with stage 1 with subcompensated diabetes

Shown, that under the age of 60 is relatively the largest the average fibrinogen level was in patients on Stage 2 of the DRP (especially for CI - 446.1 μg / dl), and over the age of 60 years - at the 3rd stage of the PSA (including number on the confidence interval - 458.2 mcg / dl).Worst average fibrinogen levels in these comparison groups was observed in patients after the age of 60 years at the 3rd stage of PSD (390.0 mcg /dl), data are reliable in comparison with the 1st stage at the age of patients up to 60 years. Along with this, according to regression analysis an upward trend was identified (p = 0.9) fibrinogen concentrations with age in patients with type 2 diabetes and DRP (n = 56) (r = 0.22; R2 = 5.2%)

In patients with diabetes lasting up to 10 years the highest fibrinogen level was in patients at the 3rd stage of DRP, only by CI - 415.4 μg / dl, while patients with diabetes lasting more than 10 years - also at the 3rd stage of the DRP (including the CI - 470.1 μg / dl). Worst average fibrinogen level in these comparison groups was observed in patients with diabetes lasting more than 10 years also at the 3rd stage of DRP (391.6 μg / dl), data have a degree of certainty in the form of a distinct strong trend compared to stage 1 with diabetes lasting up to 10 years.

Based on the regression analysis was revealed that fibrinogen level is moderate increased with increasing duration diseases in patients with DRP (n = 56) with parameters regression curve: r = 0.38; R2 = 14.4%; p = 0.03. It should be noted a direct nonlinear nature correlation of fibrinogen concentration with a duration of type 2 diabetes. That pays attention the fact that the dynamics of change is most pronounced during the first 10 years of diabetes (see picture).

In patients with HbA1C ≤8% relative the highest average fibrinogen level was in patients at the 3rd stage of DRP (including CI - 450.5 μg / dl), and with HbA1C more than 8% - also at the 3rd stage of the DRP the same for DI - 425.0 μg /dl). Relatively Worst Average fibrinogen in these comparison groups observed in patients with HbA1C less than 8% on the 3rd stage DRP (373.6 μg / dl), data reliable compared to stage 1 with subcompensation diabetes.

Overall, the most clinically significant hyperfibrinogenemia is noted at the age of patients over 60 years (exceeding permissible values by 31%), with a duration of diabetes more 10 years (34% excess), with subcompensation Type 2 diabetes (HbA1C less than 8%) (excess by 29%) - at the proliferative stage of DRP, which partially supported by statistically significant differences and / or a clear tendency towards increased levels of fibrinogen in the blood compared with the non-proliferative stage.

According to literature, more than half patients with DRD and MS detected hyperfibrinogenemia, and the average concentration blood fibrinogen significantly higher in patients with type 2 diabetes with MS compared with diabetic patients without MS (p <0.001) [8]. To check the hypothesis that high concentrations fibrinogen baseline associated with the onset or progression of DRP, in a widely a famous study by US veterans (Veterans Affairs Diabetes Trial, VADT) morbidity and progression analysis DRP by sorting and evaluating stereoscopic half-focus fundus images of both eyes at the beginning and 5 years after the start of the study (858 participants out of 1,791) [4]. Vadt was open prospective randomized controlled research to verify the effects of standard glycemic control (STD) versus intensive control (INT) on cardiovascular events in patients with progressive type 2 diabetes. Was a reliable relationship between fibrinogen level and type of antidiabetic therapy, namely: INT was associated with a decrease progression of retinopathy in patients with blood

fibrinogen <296 mg / dl (OR 0.55 [95% CI 0.31-1.00], p = 0.03). In our study based on regression analysis was significant (p = 0.03) positive nonlinear association of fibrinogen level and the duration of the disease in patients with DRP and especially during the first 10 years from the onset of diabetes. Therefore, our results complement VADT study on role fibrinogen in the progression of DRP.

CONCLUSIONS

1. With the progression of DRP from non-proliferative to proliferative stage with type 2 diabetes as a component of MS occurs significant increase in concentration fibrinogen in the blood.

2. Identified reliable positive nonlinear association of blood fibrinogen concentration and duration of type 2 diabetes, especially throughout the first 10 years from the onset of the disease.

3. A modifying effect on blood fibrinogen concentration in patients with type 2 diabetes type only for the proliferative stage of DRP such factors like older patients, degree compensation for carbohydrate metabolism in severe trends in the participation of diabetes duration factor.

Authors declare no conflict interests.

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MARKERS OF LIVER DAMAGE IN COMORBIDITY OF NON-ALCOHOLIC LIVER DISEASE AND HYPERTENSION

Summary. Objective: to study the features of liver damage and to study the main factors of influence on this process with comorbidity between non-alcoholic fatty liver disease and essential hypertension or renoparenchymal arterial hypertension.

Materials and methods. The object of the study was 269 patients, included in three groups: group 1 - patients with non-alcoholic fatty liver disease (60 patients), group 2 - patients with comorbidity of non-alcoholic fatty liver disease and essential hypertension (121 patients), group 3 - patients with comorbidity of non-alcoholic fatty liver disease and renoparenchymal arterial hypertension (88 patients). The control group consisted of 20 healthy individuals of the same age and gender categories. Clinical examination of patients included an assessment of the parameters of an objective examination: in particular, anthropometric data and blood pressure according to standard methods. We studied both laboratory and instrumental markers of liver damage. To diagnose the