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Research Article

Comparative Evaluation of the Influence of the Factors of the Progress of Diabetic Retinopathy on the Procoagulating Potential of Blood at Metabolic Syndrome

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Abstract

Objective: To study the concentration of the serum blood fibrinogen at different stages of diabetic retinopathy (DRP) and to make a comparative evaluation of the effect of the factors of the progression of DRP on the procoagulant potential of blood at metabolic syndrome (MS).

Materials and Methods: The research was carried out on 64 patients (95 eyes) with type 2 diabetes (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/m^2), who were divided into 3 groups depending on the stage of DRP. HbA1C was estimated by liquid ion exchange chromatography with high pressure, total cholesterol and its fractions - using the method of spectrum photometry, fibrinogen - using the clotting method. Patients underwent complex ophthalmological examination: autorefractometry, visometry, tonometry, perimetry, biomicroscopy, fundus photography and fluorescein fundus angiography. We use 3 main stages for diabetic retinopathy: non-proliferative, pre-proliferative and proliferative. 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 8%) (exceeding by 29%) and with the use of insulin therapy (exceeding by 28%) - in the proliferative stage of DRP.

Conclusions: With the progression of DRP from non-proliferative 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 1st stage vs 368,6 ± 23.8 μg/dl, 95% CI 334.7 - 402.3 μg/dL - the 3-rd stage, $P^2 < 0.05$). A reliable positive nonlinear association of the blood fibrinogen concentration with T2D duration ($r = 0.38$, $R^2 = 14.4\%$, $p = 0.03$) was revealed, especially during the first 10 years from the onset of the disease.

Keywords: *Diabetic Retinopathy; Fibrinogen; Metabolic Syndrome*

Introduction

Metabolic syndrome (MS) is traditionally characterized by dyslipidemia, high blood pressure, abdominal obesity, hyperglycemia, and insulin resistance [1,2]. However, it is currently believed that MS is also associated with the level of fibrinogen, uric acid, C-reactive protein, leptin, interleukins in the blood and endothelial dysfunction [3]. The combination of MS with a cluster such as hyperfibrinogenemia

increases the risk of micro- and macrovascular complications, including diabetic retinopathy [4], which indicates the relevance of further research on the relationship of fibrinogen level with the risk of developing and progression of diabetic retinopathy (DR) in diabetes type 2 diabetes mellitus and MS.

Aim of the Study

To study the concentration of fibrinogen in the blood serum at various stages of DR and to conduct a comparative assessment of the influence of the factors of the progression of DR on the procoagulatory potential of blood in MS.

Materials and Methods

Studies were conducted in 64 patients (95 eyes) with MS, type 2 diabetes and DR (men and women, mean age 61.55 ± 2.37 years, mean length of diabetes 11.23 ± 2.11 years, average the level of glycated hemoglobin (HbA1C) is 9.89 ± 0.78%, the average body mass index (BMI) is 34.55 ± 3.75 kg/m^2), which were divided into 3 groups depending on the stage of DR. The control group consisted of 16 people overweight or obese without diabetes (men and women, average age 61.23 ± 5.46 years, average BMI 32.99 ± 4.81 kg/m^2).

The work was performed in accordance with the requirements of the Helsinki Declaration of the World Medical Association (2008), the orders of the Ministry of Health of Ukraine No. 281 of 01.11.2000, No. 355 of September 25, 2002, No. 1118 of December 21, 2012. Exclusion criteria from the study were: the presence of endocrine and somatic diseases leading to obesity, acute infectious diseases, type 1 diabetes, cancer, decompensation of comorbid pathology, mental disorders, taking neuroleptics and antidepressants, proteinuria, clinically significant maculopathy, damage to the optic nerve, glaucoma and cataracts [5]. In patients of the studied and control groups, growth, body weight, waist and hip volume were measured, BMI was calculated, systolic and diastolic blood pressure was recorded, and in the serum concentrations of total cholesterol, high density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C) and triglycerides (TGs), as well as fasting glucose and HbA1C (in patients with type 2 diabetes) were determined. MS was determined by the Working criteria of experts of the US National Institutes of Health (Adult Treatment Panel III, ATP III, 2001), recognized by WHO, and the consensus of the World Federation for the Study of Diabetes Mellitus (IDF) [1,6]. Plasma glucose concentration was determined by the glucose oxidase method, and in capillary blood by an enzymatic colorimetric method, HbA1C concentration in the blood - by high pressure liquid-exchange ion chromatography, the concentration of TGs, total cholesterol and its fractions - by spectrophotometric method. The procoagulative potential was assessed by the serum fibrinogen concentration, which was determined by the clotting method. The level of comparison of HbA1C taking into account the patient-oriented approach and life expectancy was selected less than 8% [7,8]. The following types of glucose-lowering therapy were distinguished: 1 - diet and administration of metformin, 2 - diet, administration of metformin and oral glucose-lowering medications (OGLMs), 3 - diet, administration of metformin and insulin therapy. All patients underwent a comprehensive ophthalmologic examination using autorefractometry, visometry, tonometry, perimetry, biomicroscopy, fundus photography and fundus fluorescence angiography (if indicated). The diagnosis of DR was set 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 DR: non-proliferative, pre-proliferative and proliferative.

Statistical processing was performed using one- and two-factor analysis of variance and regression analysis. A parametric Fisher criterion or a non-parametric Kruskal-Wallis criterion was used. Characteristics of regression models were considered: r - correlation coefficient, R^2 - coefficient of determination, p - level of statistical significance of models. Statistical characteristics are presented as arithmetic mean (M) and standard error (± m), 95% confidence interval (95% CI). Statistically significant differences were considered if $p < 0.05$. Statistical data analysis was performed using the computer program "SPSS 9.0". Calculations and graphing of curves was carried out in the statistical computer package Statgraphics 3 for Windows.

Results and Discussion

Indicators of fibrinogen in the blood of patients with MS and type 2 DM at different stages of DR are presented in table 1. As shown by the results of analysis of variance, fibrinogen parameters in the blood exceeded the upper level of permissible values (less than 350 μg/dl) at the 3rd stage of DR both in mean values (368.6 μg/dl) and in CI (402.3 μg/d), and statistically significant differences were found when comparing the mean values of fibrinogen in patients at the 1st and 3rd stages of DR ($p < 0.05$). Differences in this indicator between the

main groups and the comparison group (obesity) were not identified with a clear upward trend in fibrinogen levels during the transition from stage 1 to stage 2 and already a significant increase in its concentration at stage 3 of DR.

Indicator	Statistic Indicator	Obese Persons	Patients with diabetic retinopathy		
			1st stage	2nd stage	3rd stage
		1	2	3	4
Fibrinogen, µg/dl	N	16	42	12	10
	M ± m	326,5 ± 16,4	316,4 ± 10,8	346,7± 22,5	368,6 ± 23,8
	95% DI	303,3- 349,6	301,1-331,6	314,9 - 378,5	334,7 - 402,3
					$p_2 < 0,05$

Table 1: *The average statistical concentration of fibrinogen in the blood, depending on the stage of diabetic retinopathy (N; M + m; 95% CI).*

Note: N is the number of persons in groups, CI is the confidence interval, P is the level of statistical significance (F-criterion) compared with the specified group.

Indicators of fibrinogen in the blood of patients with MS and type 2 DM, taking into account the progression factors of DR, are presented in table 2. It was shown that at the age of up to 60 years the relatively highest average level of fibrinogen was in patients at the 2nd stage of DR (especially by CI - 446.1 µg/dl), and at the age of more than 60 years - at the 3rd Stage DR (including the confidence interval - 458.2 µg/dl). The worst level of fibrinogen in these comparison groups was observed in patients after the age of 60 years in the 3rd stage DR (390.0 µg/dl).

Comparison groups	Diabetic retinopathy		
	1st stage	2nd stage	3rd stage
Age of patients ≤ 60 years	25	6	5
	310,3 ± 13,8	367,3 ± 39,2	347,1 ± 33,9
	282,4 - 338,1	288,6 - 446,1	278,9- 415,3
Patient age > 60 years	17	6	5
	326,1 ± 17,5	336,4 ± 27,7	390,0 ± 33,9
	290,8 - 361,3	280,7 - 392,1	321,8 - 458,2
Duration of diabetes ≤ 10 years	31	5	6
	318,1 ± 12,2	316,9 ± 33,8	354,7 ± 30,2
	293,5 - 342,6	248,9 - 384,8	293,9 - 415,4
Duration of diabetes > 10 years	11	7	4
	310,6 ± 22,3	370,6 ± 30,2	391,6 ± 39,0
	265,9 - 355,4	309,8 - 431,4	313,1 - 470,1
HbA_{1C} ≤ 8%	15	5	4
	289,1 ± 19,1	312,2 ± 46,8	373,6 ± 38,2
	250,7 - 327,5	218,0 - 406,3	296,8 - 450,5
HbA_{1C} > 8%	27	7	6
	331,7 ± 12,9	356,6 ± 25,0	365,5 ± 29,6
	305,6 - 357,8	306,3 - 406,9	305,9 - 425,0
OGLMs	26	5	4
	315,4 ± 13,7	317,3 ± 47,5	336,5 ± 39,3
	287,9 - 342,9	220,7 - 413,8	257,6 - 415,3
Insulin Therapy	16	7	6
	317,8 ± 17,3	355,1 ± 25,7	387,8 ± 30,4
	282,6 - 352,6	303,5 - 406,7	326,7 - 448,8

Table 2: *The average statistical data on the concentration of fibrinogen in the blood at different stages of diabetic retinopathy, depending on the factors of its progression (N; M ± m; 95% CI).*

Note: N - the number of persons in groups, CI - confidence interval, OGLMs - oral hypoglycemic drugs.

Along with this, according to the regression analysis, there was a tendency (p = 0.9) to increase the concentration of fibrinogen with age in patients with type 2 diabetes and DR (N = 56) (r = 0.22; R^2 = 5,2%).

In patients with a diabetes duration of up to 10 years, the highest level of fibrinogen in patients with Stage 3 DR has only had an CI of 415.4 μg/dl, and in patients with a diabetes duration of more than 10 years, also at Stage 3 of DR (including by CI - 470.1 μg/dl). The worst fibrinogen level in these comparison groups was observed in patients with a diabetes duration of more than 10 years also at the 3rd stage of DR (391.6 μg/dl).

Based on the regression analysis, it was found that the level of fibrinogen increased moderately with an increase in the duration of the disease in patients with DR (N = 56) with regression curve parameters: r = 0.38; R^2 = 14.4%; p = 0.03. It should be noted direct non-linear nature of the correlation due to the concentration of fibrinogen on the duration of type 2 DM. Attention is drawn to the fact that the dynamics of changes are most pronounced during the first 10 years of diabetes (See figure).

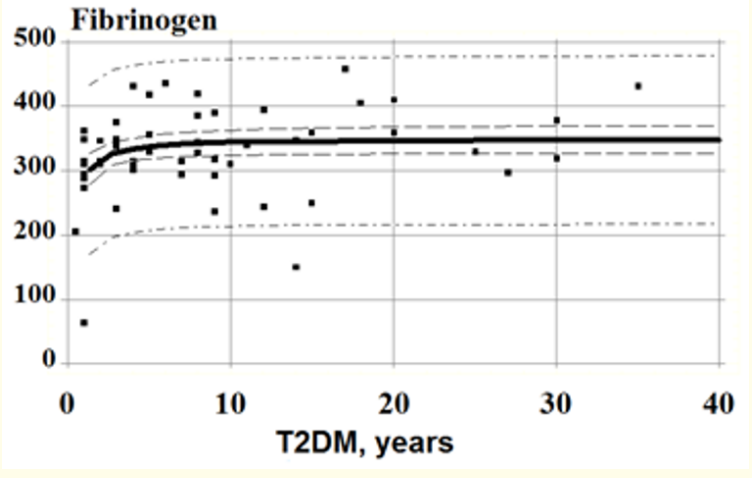

Figure: *Curve of the dependence of fibrinogen concentration in the blood on the duration of type 2 diabetes in patients with diabetic retinopathy against the background of the metabolic syndrome.*

In patients with HbA1C ≤ 8%, the highest average fibrinogen level was in patients with Stage 3 DR (including CI 450.5 μg/dl), and with HbA1C more than 8% - also at the 3rd Stage DR (also CI - 425.0 μg/dl). The relatively worst mean fibrinogen level in these comparison groups was observed in patients with less than 8% HbA1C at stage 3 DR (373.6 μg/dl).

In the treatment of OGLMs, the highest level of fibrinogen was in patients at the 2nd and 3rd stages of DR only by CI (413.8 μg/dl and 415.3 μg/dl, respectively), and when using insulin therapy - on the 3rd stage of DR (including CI - 448,8 mkg/dl). The worst average cholesterol level in the presented comparison groups is observed at the 3rd stage of DR in patients receiving insulin therapy (387.8 μg/dl).

In general, the most clinically significant increase in the concentration of fibrinogen in the blood is observed at the age of patients over 60 years old (exceeding the acceptable values by 31%), with diabetes lasting more than 10 years (exceeding 34%), with subcompensation of diabetes 2nd type (HbA1C less than 8%) (29% excess) and when using insulin therapy (28% excess) - at the proliferative stage of DR.

According to the literature, more than half of patients with DR and MS show hyperfibrinogenemia, and the average concentration of fibrinogen in the blood is significantly higher in patients with type 2 diabetes with MS compared to diabetic patients without MS (p < 0.001) [4]. To test the hypothesis that high levels of fibrinogen at baseline are associated with the onset or progression of ANC, a well-known study of US veterans (Veterans Affairs Diabetes Trial VADT) conducted a separate analysis to estimate the incidence and progression of DR by sorting and evaluating stereoscopic half-focus images of the eye the bottoms of both eyes at the beginning and 5 years after the start

of the study (858 participants from 1 791) [9]. VADT was an open, prospective, randomized controlled trial to test the effects of standard glycemic control (STD) versus intensive control (INT) on cardiovascular events in patients with advanced type 2 diabetes. A significant relationship between the level of fibrinogen and the type of antidiabetic therapy was found, namely: INT was associated with a decrease in the 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, on the basis of regression analysis, a reliable (p = 0.03) positive nonlinear association of fibrinogen level and disease duration was found in patients with DR, and especially during the first 10 years from the onset of diabetes. Therefore, our results complement the VADT study regarding the role of fibrinogen in the progression of DR.

Summing up the discussion, let us point out that a modifying effect on the level of fibrinogen in the blood of patients at the proliferative stage of DR can be exerted by older patients, longer duration of diabetes, subcompensation of carbohydrate metabolism and a feature of hypoglycemic therapy.

Conclusions

1. A modifying effect on the concentration of fibrinogen in the blood of patients with type 2 diabetes was found only for the proliferative stage of DR factors such as older patients, longer duration of diabetes, and antidiabetic hypoglycemic therapy (insulin therapy).
2. With the progression of DR from the non-proliferative to proliferative stage on the background of MS, a significant increase in the concentration of fibrinogen in the blood occurs.
3. A reliable positive nonlinear association of fibrinogen concentration in the blood and the duration of type 2 diabetes, especially during the first 10 years from the onset of the disease, was revealed.

Bibliography

1. "Executive summary of the third report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III)". *Journal of the American Medical Association* 285.19 (2001): 2486-2497.

2. Reaven GM. "Role of insulin resistance in human disease". *Diabetes* 37.12 (1988): 1595-1607.

3. Kyryliuk ML., *et al*. "Biometric and biochemical parameters of metabolic syndrome and risk of its occurrence in patients with benign prostatic hyperplasia". *Klinichna Endokrynolohiia I Endokrynna Khyrurhiia* 40 (2012): 53-58.

4. Mahendra JV., *et al*. "Plasma Fibrinogen in Type 2 Diabetic Patients with Metabolic Syndrome and its Relation with Ischemic Heart Disease (IHD) and Retinopathy". *Journal of Clinical and Diagnostic Research* 9.1 (2015): BC18-BC21.

5. Serdyuk VN and Ishhenko VA. "Morphometrial and biochemical clusters of metabolic syndrome in patients with type 2 diabetes mellitus at different stages of diabetic retinopathy". *Mizhnarodnyi Endokrynolohichnyi Zhurnal* 7.79 (2016): 69-74.

6. Grundy Scott M., *et al*. "Diagnosis and Management of the Metabolic Syndrome". *Circulation* 112.17 (2005): 2735-2752.

7. Kirilyuk ML., *et al*. "Diabetic retinopathy and sex hormone-binding globulin: hypothesis or the real relationship?" *Klinichna Endokrynolohiia I Endokrynna Khyrurhiia* 3.59 (2017): 69-76.

8. Inzucchi S., *et al*. "Management of Hyperglycemia in Type 2 Diabetes, 2015: A Patient-Centered Approach: Update to a Position Statement of the American Diabetes Association and the European Association for the Study of Diabetes". *Diabetes Care* 38.1 (2015): 140-149.

9. "Association of PAI-1 and fibrinogen with diabetic retinopathy in the Veterans Affairs Diabetes Trial (VADT)". *Journal of Clinical and Diagnostic Research* 9.1 (2015): BC18-BC21.

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