UNIFFERENTIATED CONNECTIVE TISSUE DYSPLASIA AS A POTENTIAL PREDICTOR OF ARTERIAL HYPERTENSION DEVELOPMENT IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

Ludmila Sherstyuk, Yevgen Nikolenko
V. N. Karazin Kharkiv National University, 6 Svobody Sq., Kharkiv, 61022, Ukraine,
e-mail: med@karazin.ua

The article presents the results of studies of markers of connective tissue dysplasia and the content of the main fibroblast growth factor in blood plasma in patients with type 2 diabetes. The presence of significant correlations between the studied parameters with the occurrence and progression of hypertension in patients with type 2 diabetes is established. A regression model for predicting the development of arterial hypertension is proposed in patients with diabetes mellitus.

KEY WORDS: arterial hypertension, type 2 diabetes mellitus, undifferentiated connective tissue dysplasia, basic fibroblast growth factor, prediction

НЕДИФЕРЕНЦІЙОВАНА ДИСПЛАЗІЯ СПОЛУЧНОЇ ТКАНИНИ ЯК ПОТЕНЦІЙНИЙ ПРЕДИКТОР РОЗВИТКУ АРТЕРІАЛЬНОЇ ГІПЕРТЕНЗІЇ У ХВОРИХ НА ЦУКРОВИЙ ДІАБЕТ 2 ТИПУ

Шерстюк Л. Л., Ніколенко Є. Я.
Харківський національний університет імені В. Н. Каразіна, пл. Свободи, 6, м. Харків, 61022, Україна

У статті наведено результати досліджень маркерів дисплазії сполучної тканини та вмісту основного фактору росту фібробластів в плазмі крові у хворих на цукровий діабет 2 типу. Встановлено наявність достовірних кореляцій між вивчаємими показниками з виникненням та прогресування артеріальної гіпертензії у хворих на цукровий діабет 2 типу. Запропоновано регресійну модель для прогнозування розвитку артеріальної гіпертензії у хворих на цукровий діабет.

КЛЮЧОВІ СЛОВА: артеріальна гіпертензія, цукровий діабет 2 типу, недиференційована дисплазія сполучної тканини, основний фактор росту фібробластів, прогнозування

НЕДИФФЕРЕНЦИРОВАННАЯ ДИСПЛАЗИЯ СОЕДИНИТЕЛЬНОЙ ТКАНИ КАК ПОТЕНЦИАЛЬНЫЙ ПРЕДИКТОР РАЗВИТИЯ АРТЕРИАЛЬНОЙ ГИПЕРТЕНЗИИ У БОЛЬНЫХ САХАРНЫМ ДИАБЕТОМ 2 ТИПА

Шерстюк Л. Л., Николенко Е. Я.
Харьковский национальный университет имени В. Н. Каразина, пл. Свободы, 6, г. Харьков, 61022, Украина

В статье приведены результаты исследований маркеров дисплазии соединительной ткани и содержания основного фактора роста фибробластов в плазме крови у больных сахарным диабетом 2 типа. Установлено наличие достоверных корреляций между изучаемыми показателями с возникновением и прогрессирования артериальной гипертензии у больных сахарным диабетом 2 типа. Предложено регрессионную модель для прогнозирования развития артериальной гипертензии у больных сахарным диабетом.

КЛЮЧЕВЫЕ СЛОВА: артериальная гипертензия, сахарный диабет 2 типа, недифференцированная дисплазия соединительной ткани, основной фактор роста фибробластов, прогнозирование

INTRODUCTION

Arterial hypertension (AG) is one of the most common cardiovascular diseases that

afflicts more than 1.5 billion people in the world, with almost 45 % of them being not aware of the presence of high blood pressure (BP) [1]. Hypertension is often manifested in combination with another pathology, in particular, with diabetes mellitus (DM), obesity, coronary heart disease (CHD), chronic kidney disease (CKD), heart failure (CH), and others [2–3]. The most often combination is hypertension and diabetes. The prevalence of hypertension among patients with diabetes is more than 60 %. Such a comorbidity significantly increases the risk of severe cardiovascular complications [4–5]. The presence of hypertension in patients with type 1 diabetes is associated with an increase in the frequency of severe stages of diabetic nephropathy and retinopathy; on the other hand, diabetes significantly increases the risk of emergence and developing hypertension, and hypertension is associated with a high risk of insulin resistance and metabolic abnormalities [6]. When combined with hypertension and diabetes, the risk of CHD developing increases by 2–4 times, stroke – 2–3 times, visual loss – 10–25 times, renal insufficiency – 15–20 times, gangrene of the lower extremities – 20 times [7].

Mechanisms of damage of many organs and systems in case of diabetes and hypertension are discussed by many researchers. Endothelial dysfunction due to metabolic disorders in diabetes or long-term BP increase lead to a breach of vasodilatation, thickening of the basement membrane of microvessels, metabolic disorders in extracellular matrix and initiating of large vessels atherosclerotic lesions [8–9]. Disturbance of lipid metabolism is essential as trigger factor, in addition to hyperglycemia. The immediate damaging factors may be the end products of glycolysis (AGE), products of lipid peroxidation, increased activity of angiotensin II, proinflammatory cytokines, leukocyte adhesion factors, activation of protein kinase C and others [10]. Increase of AGE, accumulation of circulating fatty acids, products of oxidative stress and dysfunction of the endothelium lead to accelerated apoptosis, reducing angiogenesis and cardiac remodeling violation [11].

S. Shakya et al. (2015) believe that the main target of hyperglycemia is hyaluronic-containing glycocalyx, located in the microvascular endothelium. Its damage leads to an increase in the adhesive properties of leukocytes and causes the formation of proinflammatory cytokines. In turn, this leads to the further development of oxidative stress and the progression of endothelial disorders with an increase in the proinflammatory cytokines release. Such a proinflammatory condition affects the function of functionally active cells (pericytes, smooth muscle cells, fibroblasts), which worsens reparative processes in vessels and tissues, including angiogenesis [12]. One of the mechanisms of the pathological effect of hyperglycemia is also thought to be the increase in the activity of prophylactic factors, in particular, TGF-β, which is a modulator of proteoglycan synthesis in the extracellular matrix [12–13]. is The increase in excretion of type IV collagen in patients with diabetes, with diabetic nephropathy and nephropathy of another genesis serves as an evidence of connective tissue metabolic abnormalities role in the extracellular matrix [14–15].

These data indicate that the target of pathological processes taking place in hypertension and diabetes is connective tissue. On the other hand, the presence of feedback is increasingly considered – the role of metabolic disorders of connective tissue in the emergence of another, in particular, vascular pathology. It is known that the connective tissue, which constitutes more than 50 % of the human body mass, carries out not only the supporting-skeleton, structural-forming, protective and reparative functions in the whole organism, but also takes part in almost all processes of metabolism. Pathological activation or inhibition of the activity of cellular elements of the connective tissue and changes in the structure of the basic substance can be the basis for the development and progression of the pathological process, the emergence of its complications and the appearance of comorbid pathology [16–17].

At this time, the disease, the characteristic feature of which is the development of connective tissue disorders, are defined as connective tissue dysplasia (CTD). The genetically determined differentiated variants of CTD are known that are Ehlers-Danloss, Marfan, Sticker's syndrome, and variants of CTD with clinical manifestations that are not

included in the clinical picture of hereditary pathology – undifferentiated CND (UCTD). Nowadays clinical variants of UCTD include numerical diseases with the presence of neurological, skeletal, cardiac, vascular, visceral, visual and other manifestations [16, 18]. The prevalence of CTD is rather high in the population, and single phenotypic symptoms are found in almost every fourth person [16, 19]. It is believed that the presence of CTD contributes to the development of another pathology. In particular, it has been established that diabetic neuropathy and nephropathy in children and adolescents with type 1 diabetes occur earlier and have severe course of disease in the presence of signs of connective tissue dysplasia [20].

Taking into account the value of the connective tissue in ensuring of the normal structure of all organs and tissues and in the processes of tissue remodeling under conditions of pathology, it is well-founded to study the role of UCTD in the development of hypertension, in particular, in patients with type 2 diabetes.

OBJECTIVE

The purpose of the study is to study the possibility of using the clinical signs of UCTD as predictors of the development of arterial hypertension in patients with type 2 diabetes mellitus.

MATERIALS AND METHODS

The study was performed on the basis of the endocrinology department of the Kharkiv Regional Clinical Hospital. The study included 90 patients aged from 35 to 45 years who were on treatment during the period of 2016–2018 years with an established diagnosis of type 2 diabetes mellitus, lasting no more than 10 years.

All patients have undergone a complex general clinical, laboratory and instrumental examination in accordance to the Order of the Ministry of Health of Ukraine No. 1118 dated 21.12.2012 «Unified clinical protocol of primary and secondary (specialized) medical aid. Type 2 diabetes mellitus». The diagnosis of hypertension was carried out in accordance to the Order of the Ministry of Health of Ukraine No. 384 dated 24.05.2012, «Arterial Hypertension: An Updated and Adapted Clinical Invention based on Evidence».

Diagnosis of UCTD was carried out through a comprehensive examination and evaluation of the presence of internal (visceral) and external (skeletal, skin, articular) signs according to T. I. Kadurina (2009) [15].

Phenotypic (visceral and/or skeletal) signs of UCTD were found in 48 patients (Group I) among the patients included in the study and 42 patients had no signs of UCTD (Group II). The control group consisted of 20 practically healthy people – donors with an average age of 36.3 ± 3.1 years.

The study of the concentration of the basic fibroblast growth factor 2 (FGF2) in blood plasma was carried out by immunoassay using a Quantikine (Human FGF basic immunoassay) reagent kit manufactured by R&D Systems, Inc. (USA) on the semi-automatic analyzer ImmunoChem 2100 in the Department of Experimental Pharmacology and Toxicology of the the the SI «V. Danilevsky Institute for Endocrine Pathology Problems of the NAMS of Ukraine».

The obtained results were processed using the package of statistical software PSSR (an open-source program that does not need a license). Quantitative data is given in the form of $M \pm SD$ (average and standard deviation of the mean) for normal data distribution or Me [Q_{25}–Q_{75}] (median – 25th and 75th quarters) with abnormal data distribution. The normality of distribution was determined by the Kolmagorov-Smirnov criterion, amended by Liliefors. Quantitative indices with normal distribution were compared using Student's t-test, with an abnormal distribution – according to the Mann-Whitney criterion. The frequency of quality indicators was performed using criterion χ^2. Correlation analysis performed according to Pearson criteria.

RESULTS AND DISCUSSION

It was found that the average duration of the disease did not differ significantly and was in the 1st group (5.1 ± 2.3 years), in the 2nd group it was 4.2 ± 2.6 years (p = 0.108 per t-criterion) according to the analysis results of the peculiarities of the course of diabetes. There was 37 (77.1 %) patients with a duration of diabetes up to 5 years in Group I and 29 (69.0 %) in group II, 11 (22.9 %) patients with a duration of disease from 5 to 10 years in group I, 13 (31.0 %) – in the 2nd group ($\chi^2 = 0.740$, p = 0.390) (tab. 1).

Table 1

Features of diabetes mellitus based on the presence of UCTD

Indicator	Group I (n = 48)	Group II (n = 42)	p
Duration of DM, years	5,1 ± 2,3	4,2 ± 2,6	0,108[1]
Duration of DM: up to 5 years 5–10 years old	37 (77,1 %) 11 (22,9 %)	29 (69,0 %) 13 (31,0 %)	0,390[2]
Diabetic nephropathy – Microalbuminuria	38 (79,2 %) 17 (35,4 %)	20 (47,6 %) 6 (14,3 %)	0,002[2] 0,040[2]
Diabetic retinopathy	25 (52,1 %)	16 (38,1 %)	0,184[2]
Diabetic neuropathy	41 (85,4 %)	30 (71,4 %)	0,105[2]

Notes: 1 – the significance of the difference based on the t-criterion. 2 – the significance of the difference by criterion χ2. 3 – the significance by the Mann-Whitney criterion

Diabetic nephropathy was a frequent complication of diabetes in the analyzed sample of patients. It was diagnosed in 38 (79.2 %) patients in group I, in 20 (47.6 %) patients in II group ($\chi2 = 9,729$, $p = 0,002$). While microalbuminuria (MA) was observed in 17 (35.4 %) patients in group I and in 6 (14.3 %) patients in group II ($\chi2 = 4,205$; $p = 0,040$).

Thus, there is more severe course of diabetes with more frequent development of diabetic nephropathy with MA, as well as with the tendency to increase the incidence of diabetic neuropathy and retinopathy in patients with the signs of the UCTD.

The most common accompanying pathology in the analyzed group of patients was hypertension, which was detected in 45 (93.7 %) patients in group I, including: stage 1 hypertension – in 25 (52.1 %), stage 2 hypertension – in 17 (35.4%) and stage 3 hypertension – in 3 (6.3 %) patients. Hypertension was detected in 22 (52.4 %) patients in the II group including: 16 (38,1 %) patients with stage 1 hypertension, 5 (11,9 %) – with stage 2 hypertension, 1 (2.4 %) – with stage 3 hypertension ($\chi2 = 21.783$; $p < 0.001$) (fig. 1).
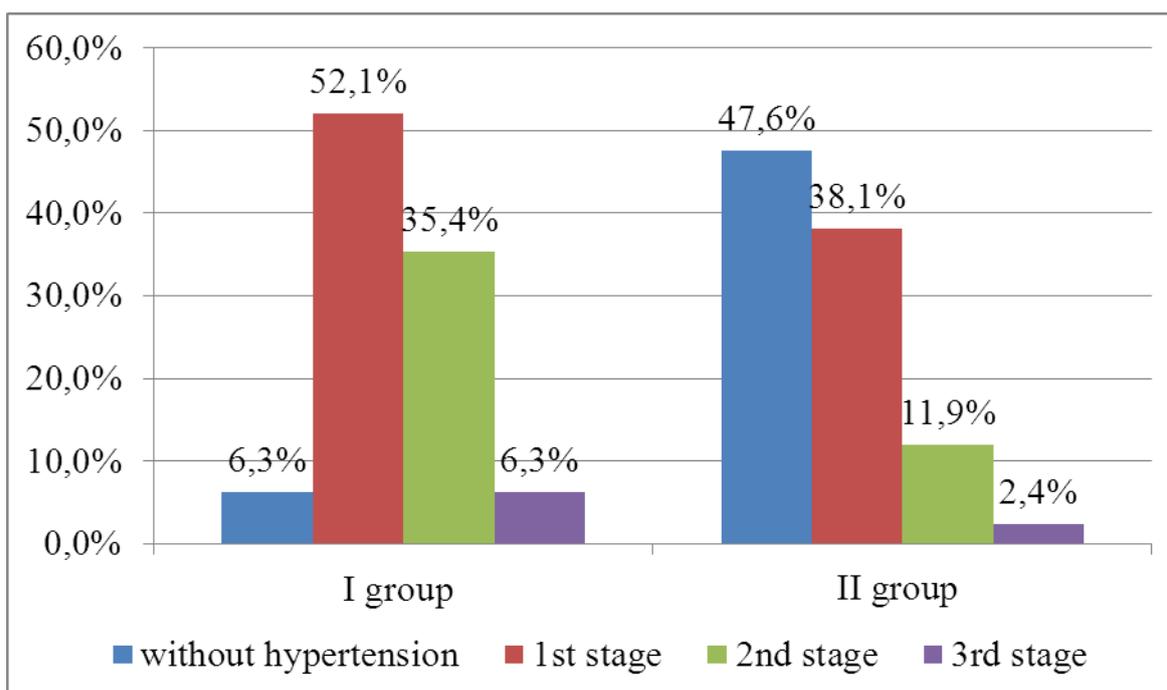

Fig. 1. Frequency and severity of hypertension in I and II groups of patients

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Certain patterns have been identified depending on the duration of diabetes as a result of the analysis of the frequency and severity of hypertension. No differences in the frequency of hypertension of varying stages depending on the duration of diabetes was detected in group I (with the presence of UCTD) ($\chi 2$ = 1,603; p = 0,659). On the contrary, clear dependence of hypertension stages on the duration of diabetes can be traced in patients of II group (without phenotypic signs of UCTD) – the frequency of hypertension itself and 2nd and 3rd stages significantly increases ($\chi 2$ = 17,961; p < 0,001) in patients with a duration of diabetes from 5 to 10 years in comparison with patients whose disease lasted less than 5 years old. These patterns are confirmed by the results of the correlation analysis: a very weak positive correlation was found at the level r_S = 0.091 (p = 0.538) in the I group and there was a significant positive correlation at r_S = 0.522 (p < 0.001) in the II group.

The comparison of frequencies of UCTD cases was performed depending on the presence of visceral and/or skeletal signs for a more detailed study of the effect of UCTD on the development of hypertension in patients with type 2 diabetes. Only visceral signs of UCTD were detected in 31 patients in the Ia group, visceral and skeletal symptoms were detected in 17 patients who were Ib group (fig. 2).
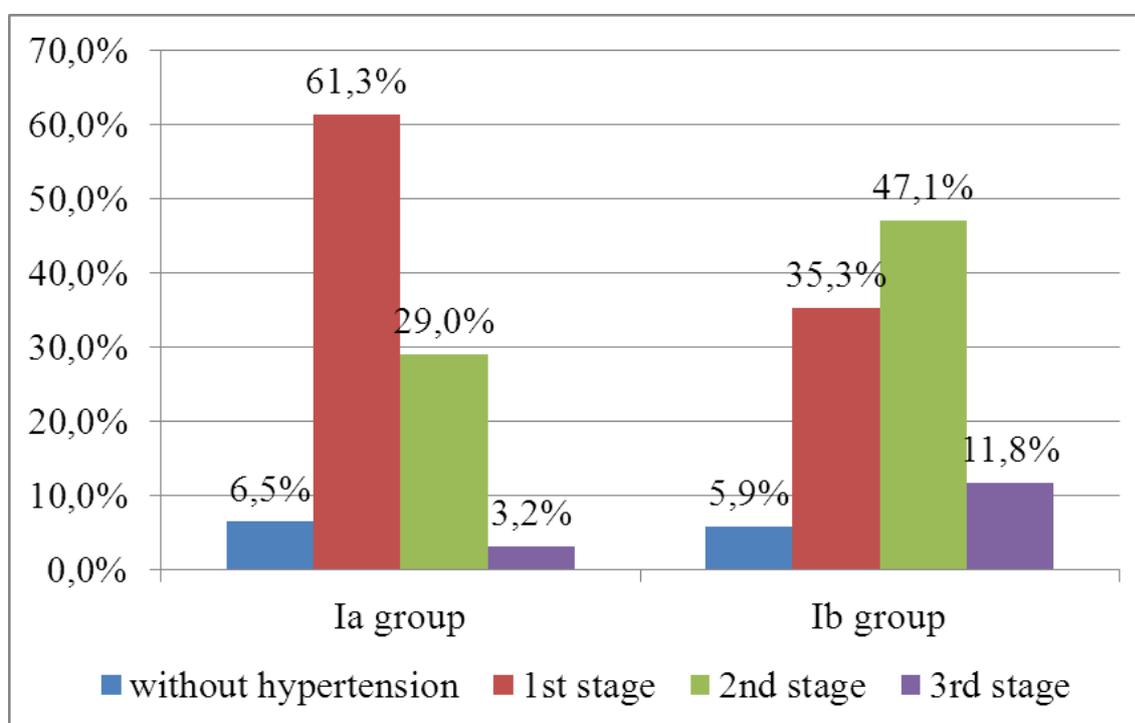

Fig. 2. Frequency of hypertension depending on the type of UCTD

Hypertension was found almost with the same frequency in both groups, but its structure differed based on stages. Stage 1 hypertension was detected in 19 (61.3 %) patients in the Ia group, stage 2 – in 9 (29.0 %) patients, stage 3 – in 1 (3.2 %). In Ib group, stage 1 hypertension was established in 6 (35.3 %) patients, stage 2 – in 8 (47.1 %), stage 3 – in 2 (11.8 %). That is, an insignificant tendency to the development of more severe stages of hypertension due to the increase in number of phenotypic signs of UCTD, in particular skeletal anomalies, is traced ($\chi 2$ = 3.718; p = 0,294).

The results of studies of FGF2 content in blood plasma are shown in tab. 2. All patients with diabetes included in the study have significantly higher median of the content of FGF2 than in the control (p < 0.05 by the Mann-Whitney criterion). The content of FGF2 was significantly higher in group I than such of controls or in group II (p < 0.05 according to the Mann-Whitney criterion in both comparisons). No significant differences were observed between subgroups Ia and Ib,

but there was a tendency for FGF2 to increase in patients of Ib group (with the presence of visceral and skeletal symptoms of UCTD).

Table 2

FGF2 content in the blood of patients with type 2 diabetes and in control group (pg/ml)

Groups	Me [Q$_{25}$; Q$_{75}$]	Min	Max
All patients (n = 90)	28,1 [18,7; 34,2][1]	7,4	63,2
I group (n = 48)	30,8 [21,6; 39,9][1,2]	12,8	63,2
Ia group (n = 31)	30,3 [22,6; 39,7][1,2]	12,8	56,2
Ib group (n = 17)	31,4 [20,5; 47,6][1,2]	16,2	63,2
II group (n = 42)	22,1 [16,2; 29,3][1]	7,7	41,2
Control group (n = 20)	3,6 [1,9; 9,0]	0,8	19,6

Notes: 1 – the differences are significant compared to the control (p < 0,05 according to the Mann-Whitney criterion). 2 – the differences are significant compared to the second group (p < 0,05 according to the Mann-Whitney criterion)

A correlation analysis of the FGF2 level in blood was performed separately in groups I and II (parametric Pearson method), which resulted in significant differences in the strength of the correlation relationships between the groups (tab. 3).

Table 3

Results of correlation analysis of FGF2 content and other indicators

Indicators	I group		II group	
	r	p	r	p
Age, years	0,107	0,227	0,649	< 0,001
Duration of DM, years	0,059	0,877	0,357	0,020
Hypertension (0 – no, 1–3 st.)	0,564	0,001	0,413	0,006
Diabetic nephropathy	0,206	0,159	0,372	0,015

Interesting differences have been identified as a result of the correlation analysis of FGF2 content and other indicators. The correlation of FGF2 depending on age and duration of diabetes mellitus was absent in group I – $r = 0.107$ and $r = 0.059$, respectively (p > 0.05). On the contrary, a significant strong positive correlation was found between FGF2 and age ($r = 0.649$, p < 0.001) and duration of diabetes ($r = 0.357$, p = 0.02) in group II. These patterns are shown in fig. 3, 4
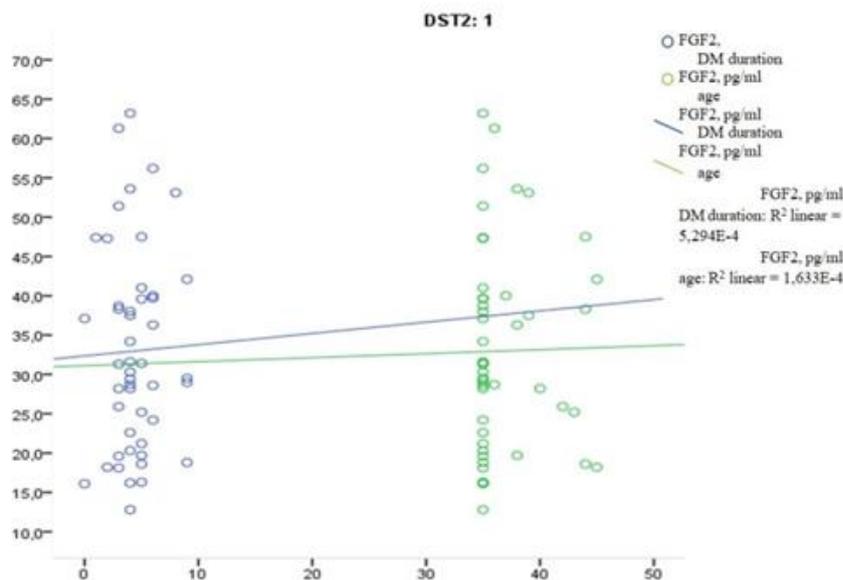

Fig. 3. Diagram of scattering of FGF2 dependence on age and duration of diabetes in I groups of patients
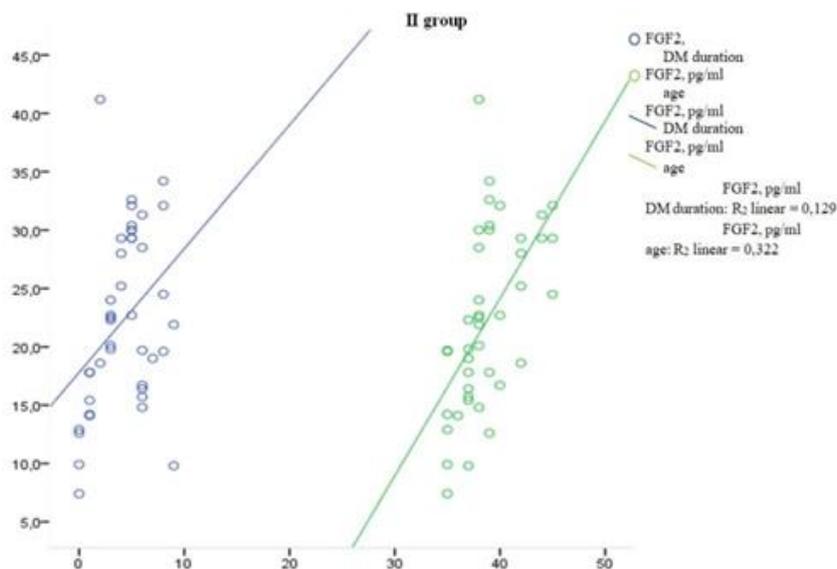
**Fig. 4. Diagram of scattering of FGF2 dependence on age and duration
of diabetes in II groups of patients**

Data suggests that the content of FGF2 increases with age and during the course of the disease in patients with DM type 2. This dependence is absent in the presence of UCTD in patients with DM type 2, which can be explained by the initial increase in the content of FGF2 on the background of metabolic disorders of the connective tissue.

Another interesting regularity is the presence of a statistically significant correlation between the content of FGF2 in patients with diabetes with the presence and severity of hypertension in both groups – $r = 0.564$ (p = 0.001) and $r = 0.413$ (p = 0.006) respectively in I and II groups.

Also, there was no significant positive correlation with the presence of diabetic nephropathy – r = 0.206 (p = 0.159) in patients with UCTD (group I). The correlation with the presence of diabetic nephropathy was significantly positive $r = 0.372$ (p = 0.015) in patients of the II group (without evidence of UCTD). In addition, the presence and severity of hypertension and diabetic nephropathy had correlations among themselves: in group I there was a significant positive correlation – $r = 0.451$ (p = 0.001), and in the second group there was also a significant positive correlation r = 0.506 (p = 001).

Thus, the presence of UCTD and increased content of FGF2 are associated with the development and progression of hypertension in patients with DM type 2, suggesting the possibility of using these indicators as predictors of hypertension. But for studying this possibility, dynamic observation for a long period since the debut of the DM is necessary. It is also needed to take into account the fairly high cost of immuno-enzymatic analysis of the content of FGF2. On the other hand, the content of FGF2 is closely related to the UCTD, therefore, the possibility of using clinical signs of UCTD to predict the development of hypertension in patients with type 2 diabetes has been tested.

To this end, an analysis of the written discharge reports after a previous inpatient treatment (from two to five years ago) was performed in patients with a duration of type 2 diabetes for at least 2 years. Such discharge reports were available in 78 patients.

The method of binary logistic regression (BLR) is used for the analysis of the possibilities of using the UCTD signs as predictors of hypertension. The patients included in this analysis were divided into two groups:

– I group – patients with DM type 2, in whom hypertension was not diagnosed during the previous hospitalizations and wasn't found during the last hospitalization, as well as patients who have no differences in degree of hypertension during the previous and last hospitalization – 38 patients;

– II group – patients with DM type 2, in whom hypertension was not diagnosed during the previous hospitalization, but during their last hospitalization hypertension was detected, as well as patients whose hypertension during the last hospitalization increased in comparison with the previous one – 40 patients.

Groups are encoded in the order scale: I group – «0»; II group – «1».

In the logistics analysis, two indicators were introduced:

– presence of signs of UCTD, encoded as the sum of individual visceral and/or skeletal symptoms – x_1.

– duration of DM type 2 in years – x_2. This indicator was introduced due to the influence of the duration of diabetes in patients with type 2 diabetes, regardless of other indicators.

According to the results of the analysis, the following data was obtained using the BLR (tab. 4).

All regression coefficients of the indicators included in the equation are reliable, with the value of significance <0.05 for all indices and constant as an evidenced, while the regression coefficient of UCTD has a very high significance < 0.001 and significantly higher than the duration of the DM. This indicates a rather high predictive value of UCTD in the development of hypertension.

Table 4

**Results of regression analysis of the hypertension development
or progression in patients with type 2 diabetes**

Indicator	B	S.E.	Wald Statistics	Sign. (p)
x_1	2,970	0,689	18,578	0,000
x_2	0,470	0,204	5,320	0,021
Constant	-4,520	1,367	10,927	0,001

Notes: x_1 - signs of UCTD; x_2 - duration of type 2 diabetes; B - coefficient of regression B; S.E. - standard error of the regression coefficient; p - level of significance of the regression coefficient.

The obtained data allow us to calculate the value of z, which can be presented in this analysis as:

$$z = x_1 \cdot 2{,}970 + x_2 \cdot 0{,}470 + (-4{,}520) \quad (1)$$

Further calculation of the hypertension development or progression probability of is carried out according to the formula:

$$P = \frac{1}{1 + e^{-z}} \quad (2)$$

(2)

The greater final value of P is, the greater likelihood of hypertension or its progression in patients with DM type 2. The critical value, which determines the patient with risk of hypertension, is 0.5.

While checking the predictive ability of the generated equation to predict the onset or progression of hypertension, the following data are established (tab. 5)

Table 5

Table of classification of observed and predicted values

Observed value		Estimated value		
		Development of hypertension		Percentage of correct
		0 (no)	1 (yes)	
Development of hypertension	0 (no)	34	4	89,5
	1 (yes)	5	35	87,5
Total percentage				88,5

Notes. Distinguishing value = 0.500

The data obtained indicate that the predictive value of the negative outcome is 89.5 %, the predictive value of the positive result is 87.5 %, and the overall predictability is 88.5 %. In 34 (87.2 %) cases out of the 39 patients who had no development or

progression of hypertension, patients received a correct prediction that characterizes the specificity of the BLR equation. A correct prognosis was obtained as well in 35 (89.7 %) cases out of the 39 patients who had hypertension or progression that characterizes the sensitivity of the BLR equation.

Sufficiently high values of predictability, specificity and sensitivity suggest that this method can be used to predict the onset or progression of hypertension in patients with type 2 diabetes and to identify patients who require active prophylaxis of hypertension, even in the absence of other cardiovascular risks.

CONCLUSIONS

1. The development of hypertension in patients with DM type 2 in combination with UCTD occurs earlier, is almost independent of the duration of diabetes, more pronounced hypertension is observed in patients with visceral and skeletal symptoms of UCTD. This is evidence of the role of UCTD in the pathogenesis of hypertension in patients with type 2 diabetes.

2. Essential role in the emergence and progression of hypertension in patients with DM type 2 is played by metabolic disorders of the connective tissue that manifests as clinical signs of UCTD. FGF2, which content is increased in patients with visceral and/or skeletal symptoms of UCTD, is involved in its pathogenesis.

3. The regression model of the prediction of hypertension in patients with DM type 2 with an assessment of the presence of UCTD signs and the duration of diabetes has a high prognosticity, specificity and sensitivity, which makes it possible to apply this method in clinical practice to determine patients with high risk of development of hypertension.

PERSPECTIVES FOR FUTURE STUDIES

The data limitation is the age group (from 35 to 45 years) and the duration of diabetes (less than 10 years). In addition, the forecasting results were obtained based on the analysis of retrospective data. More evidence may be obtained in a prospective study involving more patients with more extensive inclusion criteria.

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