OPTIMIZATION OF THE PREDICTION OF ARTERIAL HYPERTENSION DEVELOPMENT IN THE PATIENTS WITH TYPE 2 DIABETES MELLITUS ON THE BACKGROUND OF UNDIFFERENTIATED CONNECTIVE TISSUE DYSPLASIA

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Abstract. In recent years, disorders of connective tissue metabolism that are involved in the pathogenesis of many diseases have attracted increasing attention. They are of particular importance in the presence of connective tissue dysplasia. Undifferentiated forms, being a frequent component of comorbid pathology, are quite widespread among the general population. Among comorbidities, arterial hypertension, diabetes mellitus and undifferentiated connective tissue dysplasia in various combinations are more often observed.

The objective of the research was to determine the prognostic significance of undifferentiated connective tissue dysplasia in the development of arterial hypertension in the patients with type 2 diabetes mellitus.

Materials and methods. To determine the prognostic significance of undifferentiated connective tissue dysplasia in the development of arterial hypertension, there was conducted an analysis of hospital discharge reports received by the patients with type 2 diabetes mellitus duration of at least 2 years who were treated two to five years ago. The predictive significance of the factors selected for the analysis was determined through applying the regression analysis using a logistic regression model, the Wald test.

Results. The test for coincidence of the predicted and observed values revealed that the specificity of the regression model was 87.2%, while its sensitivity was 89.7%. The overall predictability was 88.5%.

Conclusions. These are quite high indicators that allow us to apply the proposed model to detect the patients with type 2 diabetes mellitus being at high risk of arterial hypertension.

Keywords: diabetes mellitus; undifferentiated connective tissue dysplasia; arterial hypertension; prognostication.

Problem statement and analysis of the recent research

Connective tissue dysplasia (CTD) is a relatively common pathology, that co-exists with other diseases, especially cardiovascular ones. CTD is a combination of genetically determined (congenital) and acquired diseases in the presence of genetic predisposition, namely dysplastic phenotypes (undifferentiated CTD). A common feature of the diseases included in the CTD dysplastic phenotypes is a disruption of connective tissue metabolism with corresponding changes in its components [2, 4]. In case of pathology, as a result of pathological activation or inhibition of the activity of connective tissue cellular elements and changes in the structure of the main substance, the disorders of connective tissue metabolism may be the basis for the progression of the pathological process, the development of its complications and the appearance of comorbid pathology [1, 3, 7-9].

The prevalence of CTD among the population is quite high (within 2-7%), and the frequency of single phenotypic symptoms reaches 24.3% [2, 4-6].

The co-existence of CTD, including its dysplastic phenotypes, affects the clinical course of arterial hypertension (AH) and diabetes mellitus (DM) as well, and may result in the progression of these diseases and the development of complications. Thus, the presence of CTD in the patients with DM was found to contribute to the increase in the incidence of diabetic foot (40.7% and 5.7% in the control group) and diabetic neuropathy (95% and 18.2% in the control group); the development of arrhythmias, psycho-emotional disorders and myocardial damage [5, 6]; AH development in the patients with neurocirculatory dystonia [2, 4]. In the patients with DM and signs of CTD, an increase in vasopressor activity and aggregation of platelets was observed. The authors regarded it as a possible mechanism of developing diabetic angiopathy [2, 5, 6].

Thus, the phenomenon of comorbidity can be currently considered as a characteristic feature of modern pathology, the incidence of which increases with the patients' age. Among comorbidities, AH, DM and CTD in different combinations are the most prevalent ones. These diseases are characterized by the development of various cardiovascular complications that indicates the possible unity of the pathogenetic mechanisms of their development. Their study is relevant both in terms of the prognosis of their clinical course and in the terms of the identification of potential common therapeutic targets.

The objective of the research was to determine the prognostic significance of undifferentiated connective tissue dysplasia (UCTD) in the development of AH in the patients with type 2 DM.

Materials and methods

The study was carried out in the endocrinological department of the Kharkiv Regional Clinical Hospital. The study included 90 patients with type 2 DM at the age of 35-45 years who were treated during 2016-2018; disease duration was no more than 10 years.

All the patients underwent a complete physical, laboratory, and instrumental examinations according to the Order of the Ministry of Health of Ukraine dated 21.12.2012 No 1118 "A Unified Clinical Protocol for Primary and Secondary (Specialized) Medical Care. Type 2 Diabetes Mellitus." Diagnosis of AH was made in accordance with 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 made through a comprehensive examination considering the presence of its most prominent phenotypic manifestations, namely skeletal (chest deformity, scoliosis, kyphosis, cranial deformation, joint hypermobility, dislocation/subluxation of any joint, flat feet, arachnodactyly) and/or visceral ones (cardiovascular – valve prolapse, interatrial septal aneurysm, additional chords, aortic root enlargement, tortuous arteries, varicose veins, varicocele; digestive - pathological reflux, gastroptosis, coloptosis, ptosis and/or deformed gallbladder, diverticula; renal - nephroptosis, atony of pelvicalyceal system) [2].

To determine the prognostic significance of UCTD in the development of AH, there was conducted an analysis of hospital discharge reports received by the patients with type 2 diabetes mellitus

duration of at least 2 years who were treated two to five years ago. Such discharge reports were available in 78 patients. During the analysis, the attention was paid to the presence of AH during the previous hospitalizations, AH degree, the presence of the diseases specific to UCTD during the last hospitalization.

To analyse the possibility of using UCTD signs as predictors of AH development, the Wald test for binary logistic regression (BLR) was applied. The patients included in this analysis were divided into two groups:

– Group I included 38 patients with type 2 DM whose AH was not diagnosed during the previous hospitalizations and was not detected during the last hospitalization, and those who did not differ in the degree of AH during the previous and last hospitalizations;

– Group II included 40 patients with type 2 DM whose AH was not diagnosed during the previous hospitalizations; however, during last hospitalization, AH was detected, and those whose AH degree increased during the last hospitalization as compared to the previous one.

Groups were encoded in the ordinal scale: Group I – "0"; Group II – "1".

Two indicators were introduced in the logistics analysis:

- presence of UCTD signs; encoded as a sum of individual visceral and/or skeletal symptoms - x_1.

- duration of type 2 DM in years - x_2. This indicator was introduced due to the known effect of the duration of DM in the patients with type 2 DM regardless of other indicators as confirmed in our study as well.

Results and discussion

The results of the analysis using BLR are presented in Table 1. All regression coefficients of the indicators included in the equation were reliable as evidenced by the significance value <0.05 for all the indicators and constant, while the significance of the regression coefficient of UCTD was very high <0.001 being significantly higher than in DM duration. This indicated a rather high prognostic value of UCTD in predicting the development of AH.

The data obtained allowed us to calculate the z value as follows:

$z=x_1×2.970+x_2×0.470+(-4.520)$ (1)

Then, the probability of AH development or progression was calculated by the following formula:

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

As a result of the analysis, both factors, namely the presence of UCTD signs with a coefficient of 2.970 (p <0.001), and the duration of type 2 DM – with a coefficient of 0.470 (p <0.021) were included in the final equation for determining the coefficient z. This was an evidence of the direct effect of UCTD on the development of AH, and the greater significance of this factor as compared to the duration of type 2 DM.

The greater the final value of P, the greater probability of AH occurrence or its progression in the patients with type 2 DM. The critical value, that determines the patient at a risk of AH, is 0.5.

While testing the prognostic ability of the created equation to predict AH onset or progression, there was found the following (Table 2)

The data obtained indicated that the prediction of the negative result was 89.5%, the prediction of the positive result was 87.5%, the overall prediction was 88.5%.

Among 39 patients without AH development or progression, correct prediction was obtained in 34 (87.2%) cases, indicating the specificity of BLR equation. Among 39 patients with AH or AH progression, correct prediction was obtained in 35 (89.7%) cases, indicating the sensitivity of BLR equation.

Conclusions

Rather high values of predictability, specificity and sensitivity suggest the possibility of using this method to predict the onset or progression of AH in the patients with type 2 DM. The data obtained will allow identifying the patients requiring active methods of AH prevention, even in the absence of other cardiovascular risks.

Prospects for further research

However, it should be noted that the study has certain limitations, namely, a limited age group (35-45 years), the retrospective nature of the analysis, the absence of daily blood pressure monitoring in most cases, variability of the analysis depth. At the same time, these restrictions determine the prospects for further research in this direction. It is advisable to carry out a larger-scale study without age restrictions, using modern methods of objectifying blood pressure fluctuations during the day, a long-term study with the determination of the control points of data collection, as well as the identification of the most objective UCTD markers.

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Table 1. Results of the regression analysis of AH development or progression in the patients with type 2 DM

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 DM; B - coefficient of regression B; S. E. - standard error of the regression coefficient; p - level of significance of the regression coefficient.

Table 2. Classification of the observed and predicted values

Observed value		Predicted value		
		AH development		Percentage of correct predictions
		0	1	
AH development	0	34	4	89.5
	1	5	35	87.5
Total percentage				88.5

Note: distinguishing value = 0.500

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