Asian Journal of Research № 11 (11), 2017
IMPACT FACTOR
SJIF 4,1
IFS 2,7

ISSN 2433-202x
JOURNAL DOI 10.26739/2433-202x
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INTEGRAL ASSESSMENT OF THE RISK FACTORS FOR DIABETIC RETINOPATHY (CONSIDERING GENETIC MARKER) FOR PREDICTING THE PROLIFERATIVE STAGE OF DIABETIC RETINOPATHY IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

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Crossref http://dx.doi.org/10.26739/2433-202x
Issue DOI http://dx.doi.org/10.26739/2433-202x-2017-11-11
Article DOI http://dx.doi.org/10.26739/2433-202x-2017-11-11-11

Abstract: The work was initiated to perform integral assessment of diabetic retinopathy (DR) risk factors in patients with type 2 diabetes mellitus with genetic markers taken into account. Type 2 diabetes mellitus duration, hyper coagulation, VEGF gene CG genotype, arterial hypertension, compensation (HbAIc≤7%), arterial hypertension in family medical history/ smoking, obesity (BMI > 25kg/m²) and dyslipidemia are the leading DR risk factors in patients

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JOURNAL DOI 10.26739/2433-202x
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with type 2 diabetes mellitus. The lowest, intermediate and highest DR risk was found to score 90.16-123.60, 123.61-157.04 and 157.05-190.48, respectively. VEGF gene CG genotype is found more significant in DR development in patients with type 2 diabetes mellitus than classical risk factors, such as, arterial hypertension, age, diabetes mellitus compensation and dyslipidemia.

Keywords: diabetic retinopathy, type 2 diabetes mellitus, genotype.

Proliferative diabetic retinopathy is known to severely impair vision to the extent of complete loss of vision. Therefore, the timely prognostication of PDR is of paramount interest in terms of its effective prevention.

The idea measurement of risk factors is based on the establishing links between the clinical manifestation of the disease and physiological, biologic factors, as well as environmental conditions. The impact of each factor alone or their combination increases the individual risk of the disease progression. System-based prediction, one of the methods of statistical analysis, allows to predicting the studied phenomenon not only for a certain period of time but also helps to define the risk of occurrence of a complication by comparing the prognostic criteria.

It is nowadays recognized that in addition to the known metabolic (hyperglycemia, dyslipidemia) and hemodynamic factors (arterial hypertension, nephropathy), there are hereditary and molecular genetic factors that influence the development of diabetic retinopathy. The Vascular Endothelial Growth Factor (VEGF) is one of the key regulators of angiogenesis, indicative of active vascular endothelial growth and the formation of new capillaries. VEGF gene polymorphism is associated with proliferative diabetic retinopathy in the majority of groups [Alekseeva LL, 2011; Skorobogatova ES, 2003; Shadrichev FE, 2008; Shishko ON, 2013].

VEGF, secreted by retinal pigment epithelial cells in diabetes, causes the formation of new vessels and their growth, and retinal edema. It is notable that while type 1 diabetes is associated with diabetic retinopathy where neovascularization is prevailing and more common, retinal edema with loss of central vision and involvement in the pathological process of the submacular region is more characteristic for type 2 diabetes [Simu R., 2006]. Thus, VEGF plays an important role in the development of proliferative retinopathy as it

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causes neovascularization, as well as it causes a sharp deterioration of the state of the hematoretinal barrier, characterized by hyperpermeability of the retinal vessels [Gavrilenko TI, 2011; Koval SN, 2012; Ferrara N., 2009].

The purpose of the study was to carry out an integral assessment of the risk factors, including the presence of genetic markers, in the development of PDR in patients with type 2 diabetes.

Materials and methods.

The study included patients with type 2 DM from Uzbek population. All participants underwent a questionnaire-based survey. The study included the collection of anthropometric and hemodynamic data. The biochemical studies included carbohydrate metabolism (fasting and post-prandial glycemia, glycated hemoglobin-HbA1c), lipid metabolism (TC, TG, LDL, HDL), creatinine and presence of proteinuria; calculation of glomerular filtration rate and coagulation parameters were also studied in all patients with T2D.

Genotyping of all participant was performed to study the distribution of C, G alleles and CC, CG, and GG genotypes of VEGF-A gene.

In our work, we used the method of normalization of intensive parameters (NIP) by Shigan, [6] which is based on the Bayes's probabilistic method. As a normalizing value (M) we used the indicator of the prevalence of PDR - 6.8%.

The complex of assessed factors included: age, duration of diabetes, CG genotype of the gene VEGF-A, hyperglycemia-HbA1c> 7%, arterial hypertension, dyslipidemia, BMI> 30 kg / m², nephropathy, cardiovascular disease (CVD), tobacco smoking.

Given that the factors have different strength of deleterious effects, the value of the relative risk (R) for each factor was taken into account, according to the method (Shigan E.N., 1986).

The normalizing intensive parameter (NIP) was estimated for the rating of each of factors, i.e. we divided the incidence of complications in this rating by the overall incidence of complications in the population. Indicators of relative risk (R) were also determined by the scaling of each factor, i.e. the maximum value of the factor was divided by the minimum value.

Besides, for the purpose of complex assessment of the phenomenon being studied, the value of NIP (M) was multiplied by the relative risk (R), i.e. the

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integral estimate was determined by the formula X = M x R. The data of the integral estimates for PDR in men with T2D patients is presented in Table 1.

As can be seen, people at age of 61-70 years (M = 8.760), with duration of T2D 16-20 years (M = 9.103), with nephropathy (M = 11.409), smoking (M = 13.840), hyperglycemia - HbA1c> 7% (M = 8.489), arterial hypertension (M = 7.887), CG genotype of the VEGF-A gene (M = 8.823), CVD (M = 7.635), dyslipidemia (M = 7.432) and BMI> 30 kg/m2 (M = 7.033) are at the greatest risk of PDR development.

Evaluation of relative risk in patients with T2D revealed that the duration of diabetes takes the leading role in the development of PDR (R = 4.02), followed by the age in the second place (R = 2.97), and the rest, lined in order with decreasing significance: nephropathy (R = 2.68), smoking (R = 2.15), hyperglycemia -HbA1c> 7% (R = 1.94), arterial hypertension (R = 1.60), CG genotype of VEGF-A gene (R = 1.43), CVD (R = 1.19), dyslipidemia (R = 1.15), BMI> 30 kg / m² (R = 1.06).

Table 1

Integral evaluation of risk factors for development of PDR in patients with T2D with genetic marker considered

Parameters		NIP (M)	Relative risk (R)	Integral estimate		
Duration of diabetes	12 y.	2.262	4.02	9.103	9.103	36.631
	6-10 y.	7.058		28.403		
	11-15 y.	8.324		33.494		
	16-20 y.	9.103		36.631		
	over 20 y.	6.684		26.897		
Age	below 50	7.785	2.97	23.190	8.760	26.096
	51-60	6.663		19.849		
	61-70	8.760		26.096		
	over 70	2.941		8.760		
Nephropathy	yes	11.409	2.68	30.580	11.409	30.580
	no	4.256		11.409		

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Tobacco use	yes	13.840	2.15	29.884	13.840	29.884
	no	6.410		13.840		
Hyperglycemia HbAIc> 7%	yes	8.489	1.94	16.486	8.489	16.486
	no	4.372		8.489		
Arterial hypertension	yes	7.887	1.60	12.692	7.352	12.692
	no	4.901		7.352		
CG genotype of VEGF-A gene	yes	8.823	1.43	12.352	8.624	12.352
	no	6.160		8.624		
CVD	yes	7.635	1.19	9.149	7.635	9.149
	no	6.372		7.635		
Dyslipidemia	yes	7.432	1.15	8.555	7.432	8.555
	no	6.456		7.432		
BMI> 30 kg/m²	yes	7.033	1.06	7.520	7.520	8.040
	no	7.520		8.040		

After calculating the relative risk of PDR development, we determined the potential range of risk for all of the above factors. For this purpose, we summed up the minimum and maximum values for each factor and the received in result segments divided into three parts, corresponding to the risks of complication development.

Thus, the range of risk for PDR in patients with T2D comprised 90,16 - 190,48 points.

Consequently, the higher the value of the NIP, resulting from the effect of the complex of factors, the higher the probability of the risk of PDR in patients with T2D will be. Due to this fact, it is appropriate to determine the possible risk range by dividing it into sub-ranges, which will make it possible to identify patients with a different risk probability.

Thus, we have identified three sub-ranges with the following criteria:

- Low risk of PDR (90,16-123,60) - patients, with the estimated score within this range, have favorable prognosis because the risk of PDR occurrence is minimal.

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- The average risk of PDR (123,61-157,04) - the probability of occurrence of PDR is higher in patients who fall in this range, and they should be the focus of doctors.
- High risk of PDR (157,05-190,48) - the effect of the risk factors is maximal in this sub-range, and the patients who enter this group have a significantly unfavorable prognosis for the development of PDR.

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