L.L. Yavlovskaya, E.K.Husnutdinova, R.I. Schatilova,V.I.Lazarenko

THE HYPOTHESIS OF THE DEVELOPMENT OF DIABETIC RETINOPATHY IN THE YAKUTS AT TYPE 2 DIABETES MELLITUS

ABSTRACT

The authors reported the results of the examination of patients with diabetic retinopathy (DR) at type 2 diabetes mellitus (DM), ethnic Yakuts, permanently residing in the areas of the Leno-Amga interfluve to the third generation, registered in the state register of the SD of the RS (Ya).

It is assumed that the development of DR at type 2 diabetes in ethnic Yakuts is due to the fact that the genetic (internal) factors involved in the metabolism of lipids and carbohydrates, the inflammatory process and oxidative stress, under the influence of environmental risk factors and hormonal expression in a certain age period, mainly in meno- and andropause, cause metabolic disorders and oxidative stress with an energy deficit in cells with active cleavage of ATP. Further chronic course of the inflammatory process and generalized oxidative stress lead to atherogenic damage of the vascular wall, causing pathological changes inherent to DR.

Keywords: diabetic retinopathy, type 2 diabetes mellitus, polymorphic variants of genes, Yakuts, hypothesis.

On 20, December 2006 the 61st UN General Assembly adopted the UN resolution, in which for the first time in the history of the United Nations the worldwide threat of non-infectious chronic disease - diabetes mellitus (DM) and its associated complications, entailing both a high risk for health of all nations, and huge economic losseswas announced.

Priority of national health systems in the world is to reduce blindness from diabetes by one third.

According to the World Health Organization data, the incidence of diabetes doubles every 10-15 years. Annually, more than 800,000 cases of DR are registered for the first time, including an increasing number of patients with type 2 diabetes [] (Kang P., 2012). Every year throughout the world up to 40 000 patients lose their vision] (Shadrichev FE, 2012). Real growth rates of morbidity greatly exceed these data, allowing you to identify diabetes as the largest non-infectious pandemic [] (US Census Burea, 2000).

The pathogenesis of DR is based on genetic, metabolic, hemodynamic, biochemical and immunological factors [(Neroev VV Sarygina OI Levkina OA, 2009; Moshetova LK, 2012; Frank NR, 1991, Geyer O., 1997; Feghhi M. et al., 2011; Bianchi L. et al., 2012]. To date, the pathogenesis of DR and type 2 diabetes are not fully investigated due to their long and asymptomatic treatment. Simultaneously DR problem is being discussed as a natural result of the development of diabetic changes in the retina [] Nesterov AP, 1997). The problems of the etiology, clinical manifestations, hereditary and genetic characteristics, prevention and prediction of diabetic retinopathy in patients with type 2 diabetes, including in some ethnic groups have not been fully studied [] (Balasubbu S. et al., 2010; Chun MY et al., 2010). Currently, medical genetics in ophthalmology is becoming increasingly important as the fundamental science that explains the etiology, pathogenesis, clinical polymorphism of multifactorial diseases, enabling the development of prevention and treatment of hereditary diseases. Genetically determined eye diseases play a significant role in shaping the entire spectrum of hereditary diseases in different groups of population. However, their share is 30 - 46% of cases, while in Saudi Arabia it reaches up to 84%.

In the Republic of Sakha (Yakutia) from 1960 to 2003, a five-fold increase in the incidence of type 2 diabetes was noted, especially among the indigenous population. The largest share (57%) of patients with type 2 are the Yakutsof the working age of 41 - 60 years, those aged over 60 constitute 33%. Results of population studies indicate the relative genetic uniformityofthe Yakuts (Sakha) in «Tat» C - allele of the Y-chromosome, the prescription of 6100 ± 940 years [Fedorova SA].

Purpose of this research is to study the clinical and genetic aspects of diabetic retinopathy in type 2 diabetes in the Yakuts to work out a hypotheses of the disease development.

MATERIAL AND METHODS

A group of scientists under the expedition conditions surveyed the natives –the Yakuts, residing in 5 districts of Lena Amginsky interfluveof Central Yakutia (Megino-Kangalasskii, Churapchinsky, Tattinsky, Amginsky, Ust - Aldan), where the predominant ethnic group of the Yakuts accounts over 97% of total population of the territory. According to the 2010 Census, the population of the Republic of Sakha (Yakutia) amounted to 958 thousand people.,of which the share of the rural population was- 35.9%, and in the studied areas 25.3%, i.e. 70.5% of the total rural population. The largest by population is MeginoKangalasskii-ulus (district) - 8%.

We used own data of retinopathy screening of theYakutsof Leno-Amginskyinterfluve held during expedition trips in the study area, the results of ophthalmic,reographic, morphometric, clinical and genealogical and genetic methods, laser retina photocoagulation with subsequent development of hypotheses of DR development in the Yakuts.

Sampling of patients of studied groups was formed by 1500 Yakuts, residing in rural areas of Lena Amginskyinterfluveof theRepublic of Sakha (Yakutia).

Main study group comprised 129 patients with DR in type 2 diabetes, ethnic Yakuts, residing in areas of Leno-Amginsky interfluve to the third generation and registered in the state register of DM RS (Y). Search of hereditary load to the DR in type 2 diabetes was performed in 432 patients, who had relatives with DR. In 78 patients with DR in type 2 diabetes genetic studies were conducted. Laser coagulation was held in 57 patients,rheographic research of ICA system and intraocular vessels was conducted in 40 patients.

The control group was formed of 162 healthy individuals older than 40 years, ethnic Yakuts living in identical environments, who are not in relationship with patients or other members of the study group to the third generation, without clinical and laboratory signs of diabetes and a family history of retinopathy and SD, with the presence of biallelic marker «Tat» C - allele Y-chromosome.

In both groups were women older than 50 years, the Yakuts to third generation. In the study group an increased BMI,

hyperglycemia and hypertension (p ≤ 0,05) werenoted. All patients were examined by an ophthalmologist with vizometriya, tonometry, ophthalmoscopy, furthermore theywere examined by an endocrinologist and neurogeneticist.

Isolation of DNA of patients was held in FGNU «Institute of Health of the Republic of Sakha (Yakutia)» (Yakutsk, Russia). Genotyping of polymorphic variants of genes was held in conjunction with the Department of Neurogenetics National Institute of Neurological Disorders (NINDS / NIH) (Betezda, USA). Haplotypingof polymorphic gene variants and statistical processing of genetic data were held jointly with the Institute of Biochemistry and Genetics, Ufa Scientific Center, Russian Academy of Sciences (Ufa, Russia). We used polymorphic variants of groups of genes involved in the metabolism of lipids and carbohydrates LIPC (Pr-514 variants, Ser193Asn), LPL (variants Int8, Int6, ser447tyr), ADPIQ (variants 276, Y111H, 45, -11377), PPARg (variants 18, 38, 477), LEP (variant 2549 C / A); oxidative stress (protein uncoupling mitochondrial oxidative phosphorylation) - UCP 2 gene (-862, ala55val, C'UTR 3) and inflammatory actions of TNF-alfa (-308, -857, -1031, -863), IL6 (-572, - 172), RSTN (-639, -420, 156, 298). Representativeness of the received results was provided by using standard and combined research methods.

RESULTS AND DISCUSSION

As a result of the study, the majority of patients with DR had the duration of type 2 diabetes up to 5 years (Fig. 1). DR in men was noted 2 times more often in the primary diagnosis of the prior disease. At the duration of type 2 diabetes over 5 years the proportion of DR reduces.

Clinical features peculiarities of DR in type 2 diabetes in group of ethnic Yakuts were noted in the distribution ofDR detection time depending on the duration of type 2 diabetes and sex of the patients (Fig. 1).

When analyzing the distribution of DR patients' age in type 2 diabetes according to sex it was revealed that most DR susceptible persons of both sexes were at the age of 50 -59 years. In this case, both gender groups, age group of 30 - 49 years there has been a uniform distribution of DR (31.4% and 31.3%, respectively). Increase of the proportion of DR in men was determined at the age of 40 - 49 years. With increasing of age of the patients there is a decrease in the proportion of DR in men and in the age group of 70 years and over 2 times dominated women. These results confirm the literature data on the rapid decompensation of type 2 diabetes in men.

In both gender groups preproliferative stage of DRprevails.Males proliferative stage exceeds twice the stage in women. These findings point to the role and specificity of internal factors in the defeat of fundus structures in men.

DR patients with type 2 diabetes revealed hemodynamic disturbances in the form of a significant reduction in blood flow and increase of ICA structure and intraocular vascular tone as the progression of DR, in contrast to patients with type 1 diabetes. The data obtained can be used in clinical practice as a criterion for determining the evaluation of the dynamics of blood flow deficit and vascular tone. DR is clinically characterized by abnormal choroidal or retinal vasculature with lesions of retinal neurons. It is known that photoreceptor degeneration is always accompanied by a weakening of retinal arterioles [48].

Diabetic retinopathy was observed in 43% of cases, mainly from their parents and siblings. Hereditary burden was in the sons of proband men - 39% , daughters of proband women -48%,daughters of probandmen - 27%

As a result of studies for the first time an association of polymorphic variants of genes involved in lipid and carbohydrate metabolism (lipoprotein lipase (LPL), adiponectin (ADIPOQ), periksisom-proliferator-activator receptor - gamma (PPARG), inflammatory processes: interleukin-6 (IL - 6) and Factor TNF-alpha (TNF - α) and oxidative stress (uncoupling protein 2 gene / UCP-2) wasrevealed. Simultaneously differences of identified polymorphic variants of genes depending on the sex of the patients (Table 1) were revealed. The role of polymorphic variants of leptin genes (LEP), resistin (RETN) and hepatic lipase (LIPC) in the development of DR in type 2 diabetes in the Yakuts has not been established.

First in Yakut ethnic group markers of increased risk of DR in type 2 diabetes: haplotypes GTGC (-11377C / G, 45T / G, 276G / T, 331T / C) gene Adipoq, haplotype TC (-1031T / C,-863C / A) gene TNFα, haplotype AC (rs285 (A / G), rs328 (S447X, C / G)) gene LPL, polymorphic markers-866G / A, Ala55Val (C / T) and 3 ¢ UTR I / D gene UCP-2 were revealed.

It is possible that the pathogenesis of DR in type 2 diabetes are fundamental links between involutional changes in the retina, environmental factors (environment, lifestyle, social and psychological problems, quality and nutrition, dietary habits), duration, severity and extent of the main decompensation disease accompanied by metabolic syndrome provided a genetic predisposition (family polymorphism with type 2 diabetes, and haplotypes of polymorphic variants of candidate genes associated with DR), which was established by us in ethnic Yakuts. Probably as a result of a single, complex, multi-stage pathological process in the retina of a patient with diabetic retinopathy involutionary para-inflammation transfers into acute inflammation with active chronic exposure to glucose toxicity, lipotoxicity and inflammatory cytokines contributing to the development of systemic inflammation. In this acute inflammatory process causes known functional and organic damage to the basic structures of the fundus (retinal tissue, blood vessels, optic nerve).

The period of development of diabetic retinopathy, reflecting generalized microangiopathy of the patient with type 2 diabetes indicates about the severity of diabetic vascular lesions. The average duration of diabetic retinal damage in

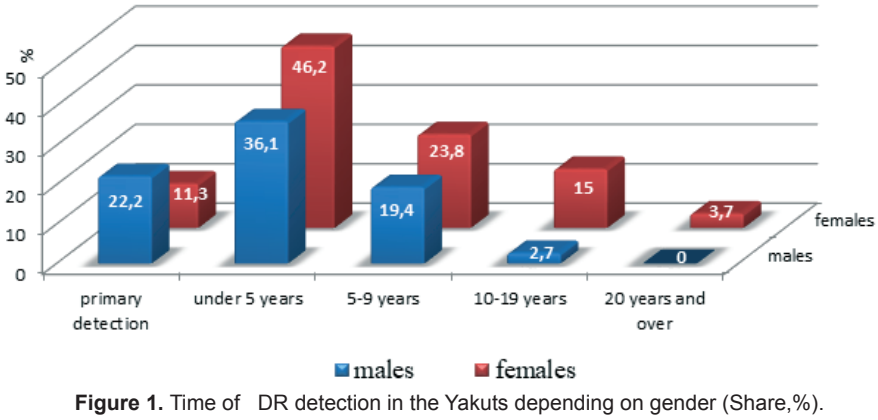

Figure 1. Time of DR detection in the Yakuts depending on gender (Share,%).

Distribution of polymorphic variants of genes depending on the duration of their expression and gender in patients with DR in type 2 diabetes

Polymorphic variants of genes / participation	Gender			Empirical term of gene expression (s
	Both sexes	Males	Females	
Gene, interleukin - 6 (IL - 6) / inflammation		aallele G rs1800796 (-572G / C) IL - 6	no	1,5
		genotype G / C allele and C Rs2234683 (-172G / C) IL - 6		
Lipoprotein lipase (LPL) / lipid metabolism	alleleArs 285 (G/A) LPL	Allele Ars 285 (G/A) LPL	alleleArs 285 (G/A) LPL	1,7 – 2,1
		Genotype CGrs 328 (C/G) LPL	no	
Tumor necrosis factor - α (TNF-α) / Inflammatory process	alleleTrs 1799964 (- 1013 T/C) TNF - α	alleleTand genotypeTTrs 1799964 (- 1013 T/C) TNF - α	alleleTrs 1799964 (- 1013 T/C) TNF – α, genotypeTTis missing	3,4
Geneofuncouplingprotein-2 (UCP-2) / oxidative stress		genotypeGA rs659366 (-866 G/A) UCP-2	Is missing	3,4
Periksisom gene-proliferator-activator receptor - gamma (PPARG) / lipid and carbohydrate metabolism		genotypeCT and allele Trs3856806 (1431C/T, Ser 477 Ter) PPARG	genotypeCCandalleleCrs1801282 (34C/G) PPARG	4,3
Adiponectin gene (ADIPOQ) / / lipid and carbohydrate metabolism		Is missing	genotypeCC rs17366743 (Y111H, 331T/C) ADIPOQ	5,6 – 6,3

the Yakuts with type 2 diabetes was 3.6 years. At the same time in one third of patients primary DR is detected in establishing primary diagnosis. At the same time long-term preservation of non-proliferative stage of diabetic retinopathy in patients with type 2 diabetes for more than 17-20 years, especially in women should be paid attention to.

Males Yakuts, unlike female Yakuts, with DR having type 2 diabetes, a fundamental factor in the development of the disease is the genetic abnormalities, associated with a greater proportion of hereditary defects in genes LPL, PPARG, IL - 6, TNF - α, UCP-2.

It is possible that such a time transfer ofDR development is confirmed in some patients with the presence of protective factors of internal body and vice versa, while in others - a genetic predisposition to the disease. It should be noted that these patients live in identical environments. However, in homogeneity of identified gender manifestations, clinical course and the presence of a genetic polymorphism in patients with DR in Yakut ethnic group have been revealed.

The obtained results of the study to identify the association of polymorphic variants of the genes of cytokines and adipokines with depression showed that in patients with type 2 diabetes gender differencesare determined .This points to the crucial role of hormonal expression and the background state of the organism of patients on the development of DR, especially during menopause and and ropause.

Uncoupling protein 2 (UCP2) is an enzyme that prevents the development of insulin cells of the pancreas and the inner mitochondrial membrane transporter, which dissipates the proton gradient, releasing the stored energy in the form of heat. Therefore, it is important in protecting against obesity. Probably provided pronounced oxidative stress also its function is impaired, which is manifested in the clinical features of the metabolic syndrome in patients with DR.

The results of our study are consistent with the opinion of the researchers on the existence of a «thrifty» genes and U-allele developed during evolution and ensuring energy supply with moderate consumption of food and hunger [].

CONCLUSION

Thus, the development of diabetic retinopathy in type 2 diabetes mellitus in ethnic Yakuts presumably due to the fact that genetic (internal) factors involved in lipid and carbohydrate metabolism, inflammation and oxidative stress, under the influence of risk factors of the environment and hormone expression in certain age period, mainly in the meno- and and ropause cause metabolic and oxidative stress with an energy deficit in the cells of the active cleavage of ATP. Further chronic inflammatory process and generalized oxidative stress lead to atherogenic damage of the vascular wall, causing pathological changes characteristic of DR. The proposed mechanism of genetically-induced diabetic retinopathy in type 2 diabetes mellitus in ethnic Yakuts is shown in the form of a scheme (Fig. 2).

REFERENCES

1. Moshetova L. Arzhimatova G. Komarov A. Kliniko-funktionalnye kharakteristiki organa zrenija pri sakharnom diabete [Clinical and functional characteristics of the organ of vision in diabetes mellitus] Vrach [Doctor]. 2012, № 5, pp.24-27.

2. Neroev V.V. Sarygina O.I. Levkina O.A. Rol' sosudistogo endotelialnogo faktora rosta v patogeneze diabeticheskoj retinopatii [The role of vascular endothelial growth factor in the pathogenesis of diabetic retinopathy] Vestn. oftalmologii [Messenger of ophthalmology], 2009, №2, pp.58-60.

3. Nesterov A.P. Diabeticheskie porazheniya organa zreniya [Diabetic lesions of the organ of vision] Probl. endokrinologii [Problems of endocrinology]. 1997, №3, pp.16-19.

4. Fedorova S.A. Geneticheskie portrety narodov Respubliki Sakha Yakutii: analiz mitohondrialnoj DNK i Y-khromosomy [Genetic portraits of the peoples of the Republic of Sakha (Yakutia): analysis of mitochondrial DNA and Y chromosome] otv. red. [edit.] Tomskiy M.I. Yakutsk: Izdatelstvo YANC SO RAN, 2008, p. 235.

5. Anciferov M.B. Mkrtumyan A.M. Suchkov S.V. [et al.] Citokiny i ih rol v patogeneze diabeticheskoj retinopatii [Cytokines and their role in the pathogenesis of diabetic retinopathy] Vestn. oftalmologii [Messenger of ophthalmology], 2010, № 6, pp.53–57.

6. Shadrichev F.E. Diabeticheskaja retinopatija: sovremennye podhody k vedeniyu pacientov [Modern approaches to managing of patients] Consilium medicum. 2012, № 12, pp.48–55.

7. Balasubbu S. Rajendran A.

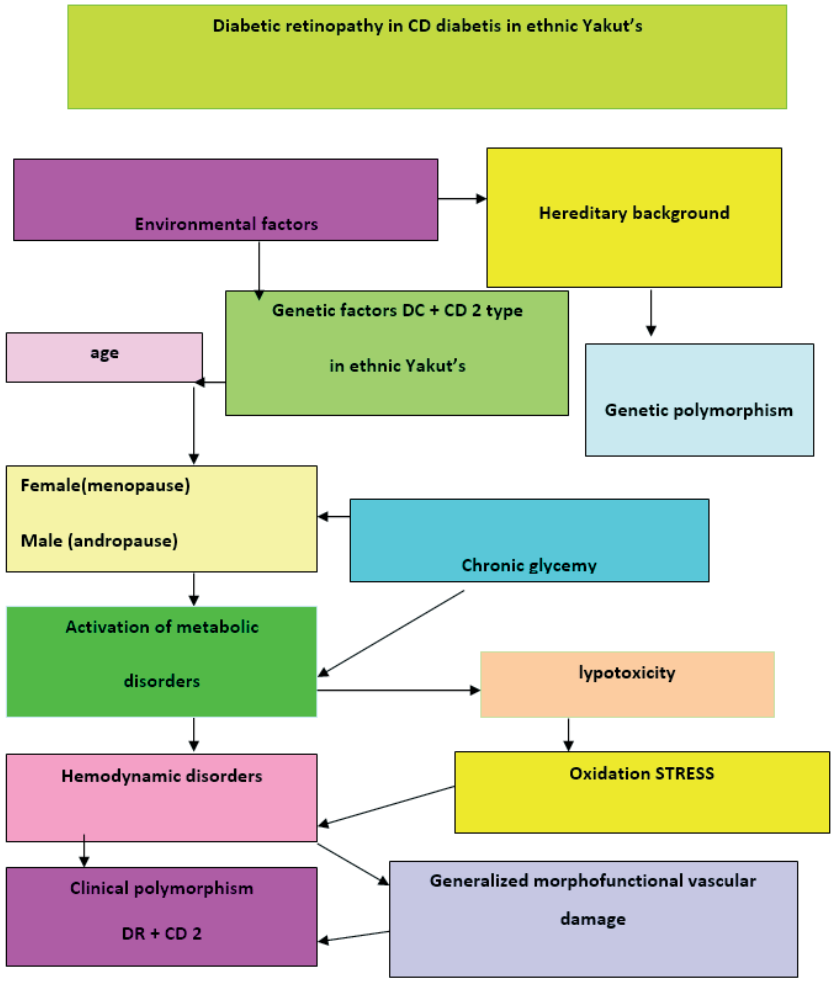

Figure 2. The mechanism of DR in type 2 diabetes in ethnic Yakut's.

Sundaresan P. [et al.] Association analysis of nine candidate gene polymorphisms in Indian patients with type 2 diabetic retinopathy. BMC Med. Genet. 2010, Vol. 11, p.158.

8. Cho H.Y. Chun M.Y. Hwang H.S. [et al.] Association of vascular endothelial growth factor polymorphisms with nonproliferative and proliferative diabetic retinopathy. Clin J. Endocrinol. Metab. 2010, Vol. 95, № 7, pp.3547–3451.

9. Gola J. Nowak A. Strzalka-Mrozik B. [et al.] Factors associated with changes in endothelin-1 gene expression in patients with diabetic retinopathy in type 2 diabetes mellitus. Mol. Vis. 2010, Vol. 16, pp.1272–1279.

10. Frank R.N. The aldosoreductase controversy. Frank R.N. Diabetes. 1994, Vol. 431, p.169.

11. Geyer O. Nitric oxide synthase activity in tissues of the bovine eye. Geyer O. Mittag T. Podos S.M. Graefes Arch. Clin. Exp. Ophthalmol. 1997, Vol.12, pp.786–793.

12. Kang P. Association of RAGE gene polymorphisms with type 2 diabetes mellitus, diabetic retinopathy and diabetic nephropathy. Jia C. Kang P. Tian C. Gene. 2012, Vol. 500, № 1, pp.1–9.

13. Esteghamati A. Feghhi M. Nikzamir A. [et al.] Relationship of vascular endothelial growth factor (VEGF) +405 G/C polymorphism and proliferative retinopathy in patients with type 2 diabetes. Transl. Res. 2011, Vol. 158, № 2, pp.85–91.

14. Choudhuri S. Dutta D. Sen A. [et al.] Role of N-epsilon-carboxy methyl lysine, advanced glycation end products and reactive oxygen species for the development of nonproliferative and proliferative retinopathy in type 2 diabetes mellitus. Mol. Vis. 2013, Vol. 19, pp.100–113.

15. U.S. Census Bureau: Profiles of general demographic characteristics 2000. United States Census 2000. Washington: Census Bureau, 2001, p.1.

THE AUTHORS

1.Lubov Leonidovna Yavlovskaya - Ophthalmological clinic of Republic Sakha (Yakutia) Healthcare Ministry , Russia, Yakutsk e mail: allu88@mail.ru;

2. Elsa Kamilevna Khusnutdinova - Corresponding Member of Academy of Sciences of Republic Bashkorcostan, Doctor of Biological Sciences, Professor, Head of the Department of the Institute of biochemistry and genetics of Ufa Scientific Centre of Russian Academy of Sciences, Ufa, Russian Federation

3. Rimma Ivanovna Shatilova-Doctor of Medical Sciences,Professor of Ophthalmological Department of GOU VPO "V.F.Voino-YasenetskyKrasoyarsk State Medical University"of Ministry of Health of Russian Federation

4. Victor Ivanovich Lazarenko-Doctor of Medical Sciences, Professor of Ophthalmological Department of GOU VPO "V.F.Voino-YasenetskyKrasoyarsk State Medical University" of Ministry of Health of Russian Federation.