DISSOCIATION OF BIOLOGICAL AGE AND BLOOD INTERLEUKINS IN PATIENTS AGED 45–59 YEARS WITH DIABETIC RETINOPATHY IN TYPE 2 DIABETES MELLITUS

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ABSTRACT

Background. *The development of diabetic retinopathy is favoured by immunological factors such as interleukins (IL) and chemokines. However, analysis of blood interleukins in patients aged 45–59 years with diabetic retinopathy in type 2 diabetes mellitus, who have biological age acceleration, has not yet been presented in publications.*

The aim of the research. *To study the content of blood interleukins in patients aged 45–59 years with diabetic retinopathy in type 2 diabetes mellitus, who have an excess of biological age over chronological age.*

Materials and methods. *241 patients aged 45–59 years with diabetic retinopathy in type 2 diabetes mellitus were examined in a clinical setting. Biological age acceleration over chronological age was found in 148 patients, biological and chronological age concorded in 51 patients. The content of interleukins in the blood was studied in all patients using an enzyme-linked immunoassay.*

Results. *The concentration of blood interleukins in patients with biological age exceeding chronological, compared with patients aged 45–59 years with concordance of biological and chronological age, was statistically significantly different for most blood interleukins and especially for IL-6, the concentration of which was 20.8 ± 1,2 pg/ml versus 3.9 ± 0.6 pg/ml, respectively ($p < 0.001$). IL-13, IL-17 were significantly increased among patients with biological age acceleration over chronological; their concentrations were 2.1 ± 0.4 and 16.5 ± 0.6 pg/ml versus 0.5 ± 0.2 and 7.9 ± 0.7 pg/ml in the comparison group ($p < 0.001$). In contrast, IL-4 and IL-10 levels were higher in patients aged 45–59 years with diabetic retinopathy in type 2 diabetes mellitus and with concordance of biological and chronological age.*

Conclusion. *IL-6, IL-8, IL-13, IL-17, IL-4 and IL-10 may serve as markers of biological age dissociation in patients aged 45–59 years with diabetic retinopathy in type 2 diabetes mellitus.*

Key words: *biological age, chronological age, diabetic retinopathy, type 2 diabetes mellitus, blood interleukins, adulthood*

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ДИССОЦИАЦИЯ БИОЛОГИЧЕСКОГО ВОЗРАСТА И ИНТЕРЛЕЙКИНОВ КРОВИ У ПАЦИЕНТОВ 45–59 ЛЕТ С ДИАБЕТИЧЕСКОЙ РЕТИНОПАТИЕЙ ПРИ САХАРНОМ ДИАБЕТЕ 2-ГО ТИПА

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РЕЗЮМЕ

Введение. *Развитию диабетической ретинопатии способствуют иммунологические факторы, такие как интерлейкины (IL) и хемокины. Однако анализ интерлейкинов крови у пациентов 45–59 лет с диабетической ретинопатией при сахарном диабете 2-го типа, имеющих ускорение биологического возраста, до настоящего времени в публикациях не представлен.*
Цель исследования. *Изучение содержания интерлейкинов крови у пациентов 45–59 лет с диабетической ретинопатией при сахарном диабете 2-го типа, имеющих превышение биологического возраста над хронологическим.*
Материалы и методы. *В клинических условиях обследован 241 пациент 45–59 лет с диабетической ретинопатией при сахарном диабете 2-го типа, среди которых выявлено превышение биологического возраста над хронологическим у 148 пациентов, у 51 пациента – соответствие биологического и хронологического возраста. У всех пациентов изучено содержание интерлейкинов в крови иммуноферментным анализом.*
Результаты. *Концентрация интерлейкинов крови у пациентов, имеющих превышение биологического возраста над хронологическим, по сравнению с пациентами 45–59 лет с соответствием биологического и хронологического возраста статистически значимо различалась по большинству интерлейкинов крови и особенно по IL-6, концентрация которого составляла 20,8 ± 1,2 пг/мл против 3,9 ± 0,6 пг/мл соответственно (p < 0,001). Значительно повышенными среди пациентов с превышением биологического возраста над хронологическим были IL-13, IL-17, концентрация которых составила соответственно 2,1 ± 0,4 и 16,5 ± 0,6 пг/мл против 0,5 ± 0,2 и 7,9 ± 0,7 пг/мл в группе сравнения (p < 0,001). Напротив, уровни IL-4 и IL-10 были выше у пациентов 45–59 лет с диабетической ретинопатией при сахарном диабете 2-го типа с соответствием биологического и хронологического возраста.*
Заключение. *IL-6, IL-8, IL-13, IL-17, IL-4 и IL-10 могут служить маркерами диссоциации биологического возраста у пациентов 45–59 лет с диабетической ретинопатией при сахарном диабете 2-го типа.*

Ключевые слова: *биологический возраст, хронологический возраст, диабетическая ретинопатия, сахарный диабет 2-го типа, интерлейкины крови, зрелый возраст*

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RELEVANCE

Diabetic retinopathy (DR) is considered one of the main complications of type 2 diabetes mellitus (DM), with an increase in incidence concurrent with the rising incidence of type 2 DM [1]. According to the International Diabetes Federation, the number of patients with diabetes mellitus has reached 463 million worldwide, and by 2045 the number of patients is expected to increase up to 700 million, with the predominance of people with type 2 diabetes mellitus [2, 3]. In our country, the prevalence of type 2 diabetes mellitus is steadily increasing, reaching 3148.5 cases per 100 thousand population. DR in type 2 diabetes mellitus leads to loss of vision and remains a serious cause of deterioration in the daily household and social activity of patients, as well as the quality of life [4, 5]. The progression of DR and a decrease in the functional activity of patients occur against the background of constant hyperglycemia and insulin resistance, which cause neurodegenerative processes and increase inflammaging [6–8].

Studies concerning changes in systemic interleukins (IL) in patients with DR in type 2 diabetes mellitus with both physiological and accelerated aging are inconsistent and ambiguous. Some publications report the involvement of IL-6, IL-10 and tumor necrosis factor α (TNF-α) in the aging process of patients with DM and DR and other somatic pathology without differentiation of aging variants [9, 10]. Other systemic interleukins, when considering the processes of premature aging in the discussed ophthalmological complication of type 2 diabetes mellitus, are usually not analyzed, although a correlation of type 2 diabetes mellitus with an increase in biological age is shown compared with chronological age, reflecting accelerated aging [11]. In this regard, it is relevant to study a wide range of systemic interleukins in patients aged 45–59 years with DR in type 2 diabetes mellitus with premature aging.

THE AIM OF THE STUDY

To study the content of blood interleukins in patients aged 45–59 years with diabetic retinopathy in type 2 diabetes mellitus, and who have an excess of biological age over chronological age.

MATERIALS AND METHODS

Clinical studies included 241 patients aged 45–59 years with DR with type 2 diabetes mellitus at Tambov Branch of the S. Fyodorov Eye Microsurgery Federal State Institution in 2020–2021. Diagnosis of type 2 diabetes mellitus and DR was carried out based on the results of a comprehensive laboratory and instrumental examination of patients and taking into account the criteria of clinical recommendations «Diabetes mellitus: diabetic retinopathy, diabetic macular edema» [12].

The verification of the diagnosis of DR was confirmed by the data of a comprehensive ophthalmological examination, including optical coherence tomography (OCT HS-100, Canon Medical, Japan), fluorescence angiography (Spectralis HRA + OCT, Heidelberg Engineering Inc., Germany), pulsed Doppler ultrasonography (Voluson 730 Pro, General Electric Healthcare, USA), determination of visual acuity without correction and maximum corrected visual acuity. Among those included in the study, 96 patients had a non-proliferative stage or form of DR, 78 people had a preproliferative stage of DR and 67 people had a proliferative stage of DR. The compared groups had no statistically significant differences in concomitant pathology. The leading concomitant diseases among patients with matching parameters of biological and chronological ages and in the group with dissociation of chronological and biological ages were arterial hypertension (34.3 ± 3.2 % and 38.5 ± 3.0 %, respectively; $p > 0.05$), respiratory diseases (18.6 ± 1.9 % and 20.3 ± 2.1 %, respectively). Kidney stone disease (13.2 ± 1.6 % and 10.9 ± 1.8 %, respectively), diseases of the musculoskeletal system (14.8 ± 2.2 % and 12.4 ± 2.0 %, respectively) were less common. Polymorbidity index in the compared groups was 2.9 ± 0.5 and 3.1 ± 0.6, respectively ($p > 0.05$). Information about concomitant pathology is obtained from official medical documentation. The patients of the compared groups also did not differ statistically significantly in the duration of type 2 diabetes mellitus.

Among 241 examined patients aged 45–59 years with DR in type 2 diabetes mellitus, biological age was determined according to the method of V.P. Voitenko et al. [13], taking into account the sex of the patient. When determining biological age by V.P. Voitenko et al. [13] method, the following indicators were determined and used: body weight (BW), systolic (SBP) and diastolic (DBP) blood pressure, pulse blood pressure (PBP), timed inspiratory capacity (TIC), static balance (SB) and self-assessed health (SAH), – according to which biological age was calculated, using the appropriate formulas for men ($BA = 26.985 + 0.125 \times SBP - 0.149 \times TIC + 0.723 \times SAH - 0.151 \times SB$) and women ($BA = -1.463 + 0.415 \times PBP + 0.248 \times BW + 0.694 \times SAH - 0.14 \times SB$). Proper biological age (PBA) was calculated using the formula: women – $PBA = 0.581 \times CA + 17.24$; for men, $PBA = 0.694 \times CA + 18.56$, where CA is the chronological age. The coefficient of aging rate was determined by the formula: BA/PBA.

Biological age was interpreted as the level of development, change or wear of the structure or function of an element of the body, a functional system, an organism as a whole, expressed in a unit of time [14]. It is believed that biological age correlates with premature (accelerated) aging [15–17], and therefore the excess of biological age over the value of the chronological age was considered by us in this work as an integral indicator of premature (accelerated) aging of patients 45–59 years old with DR in type 2 diabetes mellitus.

Based on the difference between biological and chronological (passport) age, an aging variant was established: physiological – with a difference between biological and chronological age in the range from –2.9 to +2.9 years,

accelerated (premature) – with a difference between biological and chronological age in the range of more than 3 years [14]. Taking this into account, among the examined 241 patients 51 patients with physiological aging and 148 patients with accelerated aging were identified, in whom, in accordance with the purpose of the study, the study of the systemic interleukin profile was performed using a single technique. The patients of the compared groups were comparable in terms of concomitant somatic diseases, which were in the compensation stage and could not distort the results of this study.

The content of interleukins in blood plasma was determined by enzyme immunoassay using Protein Contour kits (St. Petersburg). Blood sampling was performed before the procedures and taking medications in the morning in fasting state. The content of IL-1α, IL-1β, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-13, IL-17 was determined in blood plasma.

The examination of patients was carried out taking into account the principles of Good Clinical Practice and obtaining written informed consent of patients (Protocol No. 148-Э dated February 9, 2022).

The Statistica 10.0 programme (StatSoft Inc., USA) was used for statistical processing and the non-parametric χ^2 test was used.

RESULTS

The average chronological age in the examined cohort of patients aged 45–59 years with DR in type 2 diabetes mellitus was 51.28 ± 2.06 years (Fig. 1), and the biological age of the same group was 59.72 ± 3.41 years and statistically significantly differed from the chronological age ($p < 0.01$), exceeding the value of the latter by 8.44 ± 0.16 years. Along with other characteristics and criteria of biological age, this indicates premature aging of patients aged 45–59 years with DR in type 2 diabetes mellitus.

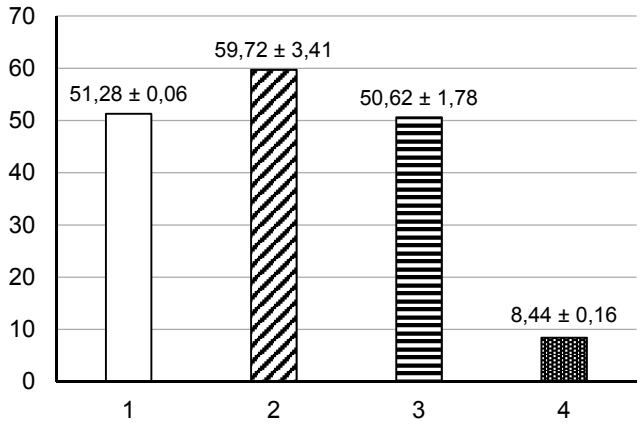

FIG. 1.

The ratio of chronological and biological age in patients aged 45–59 years with diabetic retinopathy in type 2 diabetes mellitus (M ± m, years): 1 – chronological age; 2 – biological age; 3 – proper biological age; 4 – the difference between biological and chronological age

Premature aging of mature patients with DR with type 2 diabetes mellitus is confirmed by other criteria reflecting biological age of the examined category of persons. In particular, biological age was statistically significantly higher than proper biological age, and the difference between biological and proper biological age was +9.11 ± 0.69 years. The fact that the above-mentioned difference turned out to be more than 5 years indicates accelerated aging of patients 45–59 years with DR in type 2 diabetes mellitus in accordance with the accepted grading. The statement about premature aging of patients aged 45–59 years with DR in type 2 diabetes mellitus is also based on the value of the aging rate coefficient, which reached 1.18 ± 0.02.

Biological age exceeding over chronological age reflects premature aging. It was established in 61.41 cases per 100 examined patients aged 45–59 years with DR in type 2 diabetes mellitus.

The correspondence of chronological and biological age in the same group was observed in 21.16 cases per 100 examined, which indicates the rate of normal or physiological aging, and the excess of chronological age over biological age in 17.43 cases per 100 examined, which indicates slow aging.

Consequently, type 2 diabetes mellitus and DR contribute to the acceleration of aging in most patients aged 45–59 years, realized at the cellular level by pathophysiological metabolic processes resulting from hyperglycemia and insulin resistance. Another reason for the accelerated aging of patients aged 45–59 years with DR in type 2 diabetes mellitus may be changes in the systemic interleukin profile, which we established during the study (Table 1).

Among patients 45–59 years old with DR in type 2 diabetes mellitus with biological age exceeding the chronological age, higher levels of most systemic pro-inflammatory interleukins were found relative to patients 45–59 years old with DR in type 2 diabetes mellitus with matching biological and chronological ages. Thus, the acceleration of biological age is accompanied by an increase in IL-1a, IL-3, IL-5, IL-8, IL-13, IL-17. A multiple increase in expression in patients with a biological age exceeding the chronological age is characteristic of pro-inflammatory IL-6.

However, among the anti-inflammatory blood interleukins in patients aged 45–59 years with DR in type 2 diabetes mellitus with biological age exceeding over chronological age, there was a statistically significant decrease in both IL-4 and IL-10 compared with patients 45–59 years old with DR in type 2 diabetes mellitus with matching chronological and biological ages.

The acceleration of biological age in patients aged 45–59 years with DR in type 2 diabetes mellitus did not have a statistically significant effect on the level of IL-1β, IL-2 and IL-17, the content of which was practically equivalent in both clinical groups ($p > 0.05$).

The considered results suggest an increase in the pro-inflammatory activity of systemic interleukins and inhibition of anti-inflammatory activity in patients 45–59 years of age with DR in type 2 diabetes mellitus with accelerated aging caused by biological age exceeding over chronological age, that is, due to premature aging.

TABLE 1

LEVELS OF INTERLEUKINS IN THE BLOOD OF PATIENTS AGED 45–59 YEARS WITH DIABETIC RETINOPATHY IN TYPE 2 DIABETES MELLITUS WITH ACCELERATION AND CONCORDANCE OF PARAMETERS OF BIOLOGICAL AND CHRONOLOGICAL AGE (M ± m, PG/ML)

Blood interleukins	Patients with matching biological and chronological ages	Patients with mismatch of biological and chronological ages	*p*
IL-1α	17.2 ± 0.6	20.8 ± 0.7	< 0.05
IL-1β	13.4 ± 0.9	14.6 ± 0.7	> 0.05
IL-2	2.6 ± 0.4	3.1 ± 0.5	> 0.05
IL-3	3.3 ± 0.4	5.8 ± 0.4	< 0.01
IL-4	4.2 ± 0.4	2.0 ± 0.3	< 0.001
IL-5	3.6 ± 0.2	6.2 ± 0.5	< 0.001
IL-6	3.9 ± 0.6	20.8 ± 1.2	< 0.001
IL-7	4.8 ± 0.4	6.0 ± 0.5	> 0.05
IL-8	5.6 ± 0.7	11.5 ± 0.8	< 0.001
IL-9	8.7 ± 0.6	10.0 ± 0.7	> 0.05
IL-10	17.4 ± 0.7	6.2 ± 0.6	< 0.001
IL-13	0.5 ± 0.2	2.1 ± 0.4	< 0.001
IL-17	7.9 ± 0.7	16.5 ± 0.6	< 0.001

DISCUSSION

Aging-related inflammation in conditions of systematic (chronic) hyperglycemia causes activation of pro-inflammatory cytokines [18]. In the blood plasma of elderly patients with type 2 diabetes mellitus and DR, the content of pro-inflammatory cytokines, including TNF-α, IL-6, IL-8, IL-1β, significantly increases compared with patients with a similar pathology of mature age [1]. It is noted that the levels of pro-inflammatory cytokines TNF-α, IL-6 in the blood are associated with the aging process, apoptosis, especially in patients with type 2 diabetes mellitus and DR [9, 19]. Pro-inflammatory cytokines such as TNF-α, IL-1, IL-6, IL-8 and interferon γ (IFN-γ) are the main factors of immune inflammation in DR in elderly patients with type 2 diabetes mellitus. Elevated concentrations of TNF-α, IL-1, IL-6, IL-8 and IFN-γ were found not only in the blood plasma of elderly patients with DR in type 2 diabetes mellitus, but also in aqueous humor and vitreous humor, and their change may be associated with the severity of DR [1]. At the same time, the concentration of TNF-α in patients with DR in type 2 diabetes mellitus differs significantly from that in healthy people [1]. The contribution of IL-1β to the development of DR, the level of which is increased in blood serum and aqueous humor, has been shown [20]. However, in the present study, in patients with DR in type 2 diabetes mellitus with biological age exceeding over chronological age, no statistically significant differences in the content of IL1-β were found, and there was only a tendency to increase in blood plasma.

According to researchers [21], IL-6 plays a leading role in the development of such an ophthalmological complication of type 2 diabetes mellitus as DR. It has also been shown that human aging is accompanied by a 2–4-fold increase in IL-6 in the blood [10], which can exhibit both pro-inflammatory properties, stimulating the production of antibodies and inducing an acute inflammatory process, and anti-inflammatory properties, blocking the synthesis of inflammatory cytokines [10]. The priority value of IL-6 in the accelerated aging of patients with DR in type 2 diabetes mellitus was also established in this study, which is consistent with the above-mentioned leading role of IL-6 in human aging. IL-6, from the point of view of gerontology and aging, can not only contribute to accelerated aging, but also act as a risk factor for reducing the functional reserve of the immune system and the development of life limitations [9, 10]. In addition, higher levels of IL-6 in the elderly can be considered as markers of age-associated diseases associated with accelerated aging.

In addition to the established multiple increases in IL-6 in blood plasma of patients with DR in type 2 diabetes mellitus with biological age exceeding over chronological age, statistically significant changes in other pro-inflammatory interleukins accompanied by an increase in the concentration of IL-13, IL-17, IL-8, IL-5 were diagnosed. This fact certainly indicates the involvement of the above-mentioned systemic interleukins in accelerating the aging of patients with DR in type 2 diabetes mellitus. However, it remains unclear whether inflammatory interleukins play a causal role in the pathological process of accelerated aging or act

as mediators [9]. Previous studies have shown that higher levels of inflammatory cytokines are associated with various manifestations of human aging, but these results turned out to be inconsistent and the conclusions were ambiguous [19]. Differences in the content of IL-6, TNF-α and IL-10 were found in patients with type 2 diabetes mellitus and DR compared with other somatic diseases.

Premature aging of the human body can be caused by a decrease in IL-10 in blood plasma with existing insulin resistance [7], including those established by us in patients with DR in type 2 diabetes mellitus with biological age exceeding over chronological age. It was the decrease in IL-10 among anti-inflammatory interleukins at the systemic level that turned out to be more significant in patients with DR in type 2 diabetes mellitus with accelerated aging. IL-10, produced mainly by macrophages, is responsible for suppressing the pro-inflammatory response and prevents inflammation, as well as the release and activity of inflammatory cytokines such as IL-6, TNF-α and IL-1β [6]. On the contrary, we found a lower level of IL-10 in the blood plasma of patients 45–59 years old with DR in type 2 diabetes mellitus with dissociation of biological and chronological ages, that is, with accelerated (premature) aging. At the same time, the concentration of another anti-inflammatory cytokine IL-4, whose inhibition of production was lower than IL-10, was also lower in this group. An experimental study has shown that IL-10 prevents aging-related inflammation and insulin resistance. According to this study, anti-inflammatory IL-10 plays a potential therapeutic role in the prevention of premature aging and the treatment of aging-mediated insulin resistance and helps reduce elevated levels of inflammatory interleukins circulating in the blood in the elderly against the background of aging processes.

Information on the effect of other systemic interleukins on human aging, including patients with DR in type 2 diabetes mellitus, is extremely limited, and some results were obtained on a relatively small sample of patients, the volume of which was not representative [6, 13].

CONCLUSION

Among 45–59-year-old patients suffering from DR in type 2 diabetes mellitus, with biological age exceeding over chronological age, i. e., accelerated aging occurs in more than half of cases. Patients with DR in type 2 diabetes mellitus with accelerated aging are characterized by statistically significant differences in plasma concentrations of most of the studied systemic interleukins. In patients with DR in type 2 diabetes mellitus with accelerated aging compared with patients with DR in type 2 diabetes mellitus with physiological aging, a statistically significant increase of IL-6, IL-8, IL-13, IL-17 and a decrease in the level of anti-inflammatory interleukins IL-4 and IL-10 in blood plasma. The established dissociation of interleukins shows the involvement of the immune system in accelerating the aging of patients with DR in type 2 diabetes mellitus, and the above-mentioned systemic interleukins can be used as immunological predictors of accelerated aging in such patients.

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Conflict of interest

The authors of this article declare the absence of a conflict of interest.

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