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EFFECTS OF BIOLOGICAL AGE AND AGING RATES ON THE EXPRESSION OF RISK FACTORS IN PATIENTS WITH ARTERIAL HYPERTENSION AND TYPE 2 DIABETES MELLITUS*

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The article is a fragment of the research project "Improving the diagnosis and treatment of comorbid pathology (arterial hypertension and diabetes mellitus type 2) based on the assessment of cardiac hemodynamics, metabolism and pharmacogenetic trial", state registration No. 0118U000923.

Введення: біологічному віку в останні роки відводиться велика роль у визначенні значущості та внеску в загальну концепцію факторів ризику. Актуальність визначення швидкості старіння зумовлена також тим, що швидкість старіння може мати реальне прогностичне значення для оцінки стану здоров'я як окремої людини, так і груп, що піддаються тому чи іншому фактору ризику. Метою цього проекту було вивчення біологічного віку, оцінка швидкості старіння осіб з високим серцево-судинним ризиком (CVR), а також пошук можливих співвідношень вікових показників старіння та деяких факторів ризику. Методи: протягом 2016-2018 рр. 96 пацієнтів (42 чоловіки та 54 жінки), середній вік яких склав 62,66 ± 4,21 року, з АН II стадії (тривалість захворювання 10,2 ± 3,7 року) та ДМ2Т, тривалість захворювання 4,1 ± 2,4 року) були включені в дослідження. Біологічний вік та темпи старіння досліджували за методом В.П.Войтенка та співавт. Матеріали та методи: Фізіологічне старіння спостерігалося у 9,38% (9/96) пацієнтів, у 31,25% (30/96) мав місце уповільнений темп старіння, у 59,38% (57/96) - прискорений темп старіння (ПТС). ПТС характеризувався більш вираженим індексом маси тіла, рівнем глюкози крові натще, вираженістю інсулінорезистентності. У чоловіків ПТС спостерігався в 2 рази частіше, ніж у жінок. Найбільш значущі кореляційні зв'язки між показниками, що характеризують біологічний вік і темпи старіння, були з систолічним, діастолічним і пульсовим артеріальним тиском. Таким чином, комплекс антропометричних, гемодинамічних та метаболічних порушень може виступати в ролі ініціюючого синдрому прискореного старіння, посилюючи тим самим наявний кардіоваскулярний ризик.

Ключові слова: артеріальна гіпертензія, цукровий діабет 2 типу, біологічний вік, кардіоваскулярний ризик.

Objective: biological age has been given a large role in determining the significance and contribution to the general concept of risk factors in recent years. The relevance of determining the rate of aging is also due to the fact that the rate of aging may have a real prognostic value for assessing the health of both an individual and groups exposed to one or another risk factor. The aim of the present paper was to study the biological age, to assess the rate of aging in persons with high cardiovascular risk (CVR), as well as to carry out search for possible correlations of age-related indices of aging and some risk factors. Methods: During 2016-2018, 96 patients (42 men and 54 women), whose mean age was 62.66 ± 4.21 years, with AH stage II (disease duration of 10.2 ± 3.7 years) and DM2T, disease duration of 4.1 ± 2.4 years) were included in the study. The biological age and rate of aging was investigated by the method of V.P. Voitenko et al. Results: Physiological aging was observed in 9.38% (9/96) patients, in 31.25% (30/96) there was a delayed rate of aging, in 59.38% (57/96) - an accelerated rate of aging (ARA). ARA was characterized by a more pronounced body mass index, fasting blood glucose level, insulin resistance degree. In men, ARA was observed 2 times more frequently than in women. The most significant correlations between the indices characterizing the biological age and the rate of aging were recorded with systolic, diastolic and pulse arterial pressure. Conclusion: Thus, the complex of anthropometric and metabolic disorders can act as an initiating syndrome of accelerated aging, thereby aggravating the existing cardiovascular risk.

Key words: arterial hypertension, diabetes mellitus type 2, biological age, cardiovascular risk.

Arterial hypertension (AH) and coronary heart disease (CHD) continue to be a relevant issue within the structure of cardiovascular diseases (CVD) and determine the structure of cardiovascular morbidity and mortality. The reasons for their onset and progressing are not completely understood yet, but due to scientific studies, the risk factors have been identified as contributing to their development and progression. The long-term study of various risk factors of cardiovascular diseases has led to the emergence of a concept, which is now a scientific evidence base for preventive cardiology and has been reflected in the development of various scales used to calculate the total risk and prognosis (SCORE, Framingham scale, etc.) [7,14,15]. The Committee of the European Society of Cardiology suggested to divide risk factors into non-modifiable and modifiable ones [12,14]. There are three non-modifiable risk factors: age, sex, heredity.

It is known that age is a fundamental category, but it is now believed that the chronological (calendar) age does not give a proper idea of the body's age-related damage degree and cannot serve as a reliable criterion for determining the duration of the upcoming life. Individuals of the same sex and passport age have varying degrees of age disorders in organs and systems of the body, various genetic determinants, pathological proc-

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esses occurring in the body, and have experienced a varying degree of the environmental damaging factors influence during the life [5,13]. In its turn, aging can be physiological and premature. It is believed that premature aging contributes to the early development of age-related pathology: IHD, AH, cancer, diabetes mellitus type 2 (DM2T), and the diseases onset accelerates the rate of human aging [5, 13]. Therefore, at present, the concept of biological age (BA) is used as one of the diagnostic criteria for aging, which is an integral indicator of the human health level, reflecting the reserve potential of the organism. Biological (functional) age is a fundamental characteristic of the development rate (aging), it permits to assess the degree of true aging, the level of vitality and general health of the body. By assessing the deviation of the BA from the proper biological age (PBA) - the population standard of aging, it can be judged whether the body's aging is physiological, or it is delayed, or premature [1,5]. If it is impossible to influence the calendar age, then biological age is a variable value and depends on many factors.

BA has been given a large role in determining the significance and contribution to the general concept of risk factors in recent years. This factor, apparently, transforming through well-known physiological and pathophysiological mechanisms, can either strengthen or reduce the effect of other ones, in particular, anatomical, physiological and metabolic factors. However, similar studies on representative sampling from the population have not practically been carried out. The relevance of determining the rate of aging is also due to the fact that the rate of aging may have a real prognostic value for assessing the health of both an individual and groups exposed to one or another risk factor.

The aim of the present paper was to study the biological age, to assess the rate of aging in persons with high cardiovascular risk (CVR), as well as to carry out search for possible correlations of age-related indices of aging and some risk factors.

Materials and methods

During 2016-2018, 96 patients (42 men and 54 women), whose mean age was 62.66 ± 4.21 years, with AH stage II (disease duration of 10.2 ± 3.7 years) and DM2T, disease duration of 4.1 ± 2.4 years) were included in the study. The control group consisted of 20 healthy individuals, identical to the patients by sex and age. For the patients selection, the AH diagnostic criteria, agreed with the ESC/ERS Guidelines for the diagnosis and treatment of arterial hypertension (2013) were applied [11]. The diagnosis of DMT2 has been established in compliance with the international recommendations of the American Diabetes Association and the European Association for the Study of Diabetes [9]. Against the background of dietary recommendations, all patients received basic hypotensive and antidiabetic therapy in accordance with international and national guidelines for the management of patients with the relevant pathology. [9,11]. The study did not include patients with symptomatic AH, diabetes mellitus type 1 and other endocrinological disorders, clinical signs of coronary heart disease or severe concomitant chronic diseases.

Such risk factors as body mass index (BMI), carbohydrate metabolism (fasting plasma glucose), lipid metabolism (total cholesterol (TC), triglycerides (TG), high density lipoprotein cholesterol (HDL cholesterol), low-density lipoprotein cholesterol (LDL cholesterol)), insulin resistance index (HOMA-IR), systolic (SBP), diastolic (DBP) and pulse (PBP) blood pressure were studied as modifiable. Sex was assessed as a non-modifiable risk factor.

Anthropometric indices (height, body weight, BMI calculated by the standard Quetelet formula), blood pressure level (BP) were recorded were recorded in all patients.

Laboratory studies included the determination of indicators of carbohydrate and lipid metabolism according to generally accepted methods. The concentration of insulin in the blood serum and the glycosylated hemoglobin (HbA1c) level were measured using the Hummer reagents kit (USA) by means of the immunoassay method.

Among the wide variety of methods for determining the BA, the method by V.P. Voitenko et al. has found a special distribution in many studies on the problems of aging as the most accessible and integral one [1, 2]. It consists in calculating the actual BA value for each examined patient and rationing its individual values by comparing with the estimated due value appropriate to the population standard (PBA) [1]. To calculate BA, the following indices were used: SBP, mm Hg, PBP, mm Hg, static balancing time on the left leg (SB) in seconds, time inspiratory capacity (TIC) in seconds, body weight (BW) and subjective health assessment (SHA, in relative value units), the number of adverse responses to the questionnaire that contained 29 questions and according to which SHA index was calculated. With the number of adverse answers equal to zero, health was considered ideal, with 29 - bad. The resulting SHA index value was introduced into the formula to determine the BA index. The BA calculation was carried out according to the formula:

BA of men = 26.985 + 0.215× SBP – 0.149× TIC – 0.151× SB + 0.723× SHA.

BA of women = (-1.463) +0.415× PBP–0.141×SB + 0.248× BW + 0.694× SHA.

PBA values were calculated using the formulas below:

PBA of men = 0.629×CA + 18.56; PBA of women = 0.581×CA + 17.24, where CA is the chronologic age of the individual in years.

The absolute deviation of BA from the population standard was judged by the biological age coefficient (BA-PBA), the relative deviation - by the index (BA / PBA). With BA-PBA= 0 or BA/PBA=1, the compliance of the BA with the population norm was recorded. Deviation from these values indicated accelerated or slow aging - the higher the deviation of BA from its proper value (BA-PBA>0, BA/PBA>1), the faster the individual is aging, and vice versa, the more BA lags behind DBA (BA-PBA<0, BA/PBA<1), the slower is the rate of aging [1,5].

The obtained results are presented as a mean value ± standard deviation from the mean (M±m). Statistic data processing was performed using the Statistica software package, version 8.0. To assess the differences between groups with the distribution close to normal, the Student's t-criterion and the Pearson's $\chi 2$ were used. Differences were considered statistically significant at $p < 0.05$.

The work was performed in compliance with the basic provisions of the World Medical Association (WMA) Declaration of Helsinki on ethical principles for medical research involving human subjects (1964-2000) and MOH of Ukraine Order No. 690 dated September 23, 2009.

Results and discussion

In patients with high risk, physiological aging (CA= BA) was observed in 9.4% (9/96) cases, in 31.3% (30/96)

cases, a slowed aging rate (SAR) was recorded, and an accelerated aging rate (AAR) was observed in 59.4% (57/96) patients. As evidenced by numerous studies various factors may contribute to accelerated aging [10]. Thus, Emelyanov V.V. in his study [3] shows that DM2T leads to accelerate the rate of body aging. The results of our work also confirm the opinion that the presence of associated with high cardiovascular risk (CVR) metabolic and structural changes: a significant increase in BMI, levels of TC, blood glucose, HOMA-IR, SAT, DAT compared with the control group - more often lead to the development of the accelerating aging, which in turn may become a factor that increases the total CVR.

Comparative analysis revealed that high CVR is characterized by the presence of indices characterizing the AAR (table 1). Thus, there was a significant increase in BA compared to the control group (57.41±1.30 conventional years and 50.20±1.68 conventional years, respectively, p= 0.009) and the aging rate index (1.03 ± 0.02 and 0.96 ± 0.03, respectively, p<0.05). As it can be seen from table 1, the difference between the CA and BA, which is a criterion of the aging intensity, in persons with high CVR was (-) 5.46 ± 2.25 years, while in the control group it was (-) 8.12 ± 0.97 years. However, when comparing BA to PBA, it turned out that with high CVR, BA exceeded PBA by 1.19 years, i.e. despite the fact that most people in this category are functionally younger than their CA, the biological age is still higher than that of their peers in this population.

Table 1

Comparative characteristics of anthropometric and metabolic indices of patients (M ± m) included into the study

Index	Control (n=30)	Patients with AH and DM2T (high CVR) (n=96)
Chronologic age (CA), years	58.3±1.96	62.66±4.21
Biological age (BA), years	50.20±1.68	57.41±1.30*
Proper biological age (PBA), years	50.93±0.42	56.22±0.79*
Coefficient of aging (BA-CA), years	-8.12±0.97	-5.46±2.25
Index of aging (BA/PBA)	0.96±0.03	1.03±0.02*
BMI, kg/m^2	22.12± 2.51	30.03±0.89*
Total cholesterol (TC) mmol/l	4.57± 0.42	5.64±0.21*
Triglycerides (TG), mmol/l	1.03 ± 0.30	1.91±0.14*
HDL cholesterol, mmol/l	1.45 ± 0.22	1.22±0.16
VLDL cholesterol, mmol/l	0.54± 0.22	0.85±0.08
LDL cholesterol, mmol/l	2.6 ± 0.33	3.28±0.21*
Glucose, mmol/l	4.62±1.08	8.95±0.50*
HbA1 (%)	4.62+1.08	7.62±0.20*
Insulin fasting, mulU/ml	9.8 ± 1.16	19.06±2.17*
HOMA-IR index	2.23 ± 0.36	8.26±0.68*
SBP, mmHg	125.05±3.86	146.65±2.74*
DBP, mmHg	78.19± 7.01	90.05±1.59*
PBP, mmHg.	47.03±2.02	57.59±4.91*

*Note: * - p<0.05,*
TC - total cholesterol,
TG - triglycerides,
HDL cholesterol - high density lipoprotein cholesterol,
LDL cholesterol - low density lipoprotein cholesterol,
HbA1c - glycosylated hemoglobin,
HOMA-IR - index of insulin resistance,
SBP systolic blood pressure,
DBP-diastolic blood pressure,
PBP - pulse blood pressure.

It is known that the male gender itself is a risk factor for CVD. According to gerontologists, on the basis of biological processes occurring in the male body, organic changes in tissues occur by 6 to 8 years earlier, they have more and faster developing sclerotic processes than women, i.e., biological aging of men occurs earlier and BA in men is higher [1]. When assessing the effect of gender on the aging process in our sampling, it was found that 59.3% of women (32/54) and 38, 1% of men (16/42) had SRA, while 29.6% (16 / 54) of women and 59.5% (25/42) of men were characterized by signs of accelerated aging.

Depending on the determined rate of aging, patients who had not been identified as physiological aging (n = 87) were divided into 2 groups: group 1 (n=30) - with the presence of a SRA signs and group 2 (n=57) with an ARA signs. A comparative analysis revealed (Table 2) that despite the absence of significant differences (p>0.05), fasting hyperglycemia, the increase in BMI and NOMA-IR are more associated with the ARA.

Drawing interest in this study was the fact of a more pronounced dyslipidemia in the SRA patients compared to those who have had ARA, which was manifested by higher values of TC, TG and HDL cholesterol, though these data were unreliable (p> 0.05). Perhaps the lack of a clear link between the concentration of plasma lipids and the rate of body aging in this sample of patients can be explained on the one hand, by compliance with dietary recommendations, which was one of the criteria for inclusion in this work, and on the other hand, the use of stains (atorvastatin or rosuvastatin) by majority of patients, which collectively, according to modern data, has a beneficial effect on aging processes [6].

Table 2
Comparative characteristics of anthropometric and metabolic indices in patients depending on the rate of aging

Index	Group 1 (SRA) (n=30)	Group 2 (ARA) (n=57)
BM, kg	88.40 ±3.27	92.69±2.55
BMI, kg/m^2	30.59±1.10	31.07±1.05
Total cholesterol (TC), mmol/l	5.73 ±0.44	5.32±0.27
Triglycerides (TG), mmol/l	2.15 ±0.30	1.76±0.17
VLDL cholesterol, mmol/l	0.87 ±0.09	0.99±0.23
HDL cholesterol, mmol/l	1.18 ±0.06	1.15±0.06
LDL cholesterol, mmol/l	3.66 ±0.46	3.11±0.26
Glucose fasting, mmol/l	8.83±0.71	9.14±0.31
HbA1 (%)	7.85 ±0.51	7.82±0.46
Insulin fasting, mulU/ml	16.71±0.96	19.66±2.95
HOMA-IR index	6.5±0.63	7.77±0.92
SBP, mmHg	134.73±4.01	154.09±3.7*
DBP, mmHg	84.47±2.56	94.55±1.58*
PBP, mmHg	50.27±3.02	59.55±2.90*

*Note: *p<0.05,*
TC - total cholesterol,
TG - triglycerides,
HDL cholesterol - high density lipoprotein cholesterol,
LDL cholesterol - low density lipoprotein cholesterol,
HbA1c - glycosylated hemoglobin,
HOMA-IR - index of insulin resistance,
SBP- systolic blood pressure,
DBP-diastolic blood pressure,
PBP - pulse blood pressure.

It is believed that blood pressure levels are not only one of the most important CVR factors, but it is also thought that the BP level included in all BA calculation formulas is one of the most important indicators of aging [1,4]. Thus, in our study in patients with ARA, in spite of stable antihypertensive therapy, significantly higher levels as SBP (p=0.002), as DBP (p=0.005) were found.

The elevated PBP is considered to be an independent CVR risk factor [8], and its increase is due to vascular aging, which is expressed in the reduction of vascular elasticity. Hence, in patients with high CVR, PBP levels were significantly higher than in controls (p<0.05). The distribution of patients according to the aging rate revealed that ARA patients had significantly higher PBP values (p=0.042), which could be considered as an indirect confirmation of the value of PBP as a marker of the vascular age.

Despite the lack of significant differences in lipid metabolism in patients depending on the rate of aging, the correlation analysis revealed a negative relationship between BA and TC (see table 3).

Table 3
Indices of correlation analysis in the group of patients with arterial hypertension and diabetes mellitus type 2.

Correlation	Pearson correlation	Significance (p)
BA/ TC	-0.388	0.028
BA/ SBP	0.576	0.001
Coefficient of aging / SBP	0.501	0.007
Index of aging/ SBP	0.614	0.001
BA/ PBP	0.566	0.002
Coefficient of aging / PBP	0.544	0.003
Index of aging / DBP	0.403	0.033
Index of aging / PBP	0.579	0.001

The most significant correlations between the indices characterizing BA and the rate of aging were with blood pressure indices (SBP, PBP, DBP), which again confirms the leading importance of the levels of all three investigated parameters of BP as markers of the aging process.

Conclusion

In persons with high cardiovascular risk, the predominantly accelerated rate of aging has been identified. The definition of biological age and the rate of aging in people with high cardiovascular risk is the result of a combination of age- dependent and pathological processes such as arterial hypertension, diabetes mellitus, dyslipidemia. Despite the presence in our study high cardiovascular risk in both sexes, the trend for the accelerated rate of aging in men was more pronounced than in women, suggesting that male sex can be not only a cardiovascular risk factor, but also risk factor of premature aging. The presence of the cardiovascular system pathology, in particular arterial hypertension, in combination with anthropometric (body mass index), hemodynamic (systolic, diastolic and pulse blood pressure), and metabolic (carbohydrate and lipid metabolism) disorders can act as factors that trigger accelerated aging, thus aggravating the existing level of total risk.

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