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Vascular Aging Factors in Individuals with Different Cardiovascular Risk

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Abstract

Objective: Study of vascular aging markers in conjunction with metabolic parameters and the degree of cardiovascular risk (CVR). Materials and methods: The study included 298 patients aged 40 to 69 years old. Parameters of lipid metabolism, immune inflammation, endothelial dysfunction, telomere length, insulin resistance, biological age (BA), and CVR were determined. Differences were deemed statistically significant at $p < 0.05$. Results: Significant changes occur in lipid and carbohydrate metabolism parameters, as well as markers of immune and endothelial inflammation, the degree of intensity of which depends on the CVR degree. During this process, significant changes occur in the length of telomeres, which have a relation with hyperinsulinemia. Telomeres are shorter in more than 50

Index terms— vascular aging, calendar age, biological age, cardiovascular risk, lipid profile, carbohydrate profile

1 Introduction

very year, cardiovascular diseases (CVD) are becoming more prevalent among people of both working age and old age, which leads to a significant increase in the cost of treatment of these diseases and complications, and also generally reduces the quality of life of the population. In some high-income ESC member countries, the decline in mortality from CVD has led to cancer becoming the more common cause of death, but in the middle-and low-income countries, CVDs remain the predominant cause of death (European Society of Cardiology: cardiovascular disease statistics 2017) [1]. Vascular aging has a major impact not only on the morbidity and mortality rates in people of the older age group as a whole but is also a primary risk factor for CVD. At the same time, an increase in blood pressure itself contributes to the accelerated aging of blood vessels, which predisposes to complications from the target organs through a variety of mechanisms [2]. The combination of epigenetic and genetic factors, as well as activation of the renin-angiotensin-aldosterone system, inflammation, oxidative stress, lifestyle, leads to structural and functional changes that are characterized by endothelial dysfunction, thickening, excessive fibrosis of the arterial wall, reduced elongation and arterial stiffness.

According to research data, activation of proinflammatory cytokines in the arterial wall increases with age. Also, the presence of arterial hypertension increases the synthesis of fibronectin, collagen and plasminogen-1 activator inhibitor (PAI-1), with a decrease in collagenase production, stimulation of tissue inhibitors of metalloproteinases (TIMPs), which affects the process of vascular fibrosis [3].

The leading factor in age-related diseases is oxidative stress, which aggravates vascular inflammation, supported by cardiovascular risk factors, including obesity, type 2 diabetes mellitus, metabolic disorders, etc. Increased oxidative DNA damage and increased expression of multiple biomarkers of doublestranded DNA breaks are present in atherosclerotic plaques. A violation of the mechanisms responsible for maintaining the appropriate length and functionality of telomeres plays a role in the aging of vessels and arterial hypertension, causing cellular aging [4]. Critically short telomeres can lead to cellular aging and apoptosis, which contribute to the development of atherosclerosis and predispose people to plaque instability. But telomere length is a consequence of the action of not only genetic but also environmental factors, which requires studying them in complex with other CVD risk factors and aging [5,6,7]. According to other studies, the measurement of telomeres length and telomerase

activity reflects their useful rather than harmful effect, and, thus, can serve as a surrogate marker of the vascular system [8].

Rankinen, Tuomo, et al. provide evidence of genomic sequence variants and positional genes that have a pleiotropic effect on CVD risk factors, especially the lipid profile [9].

Eaton et al. have established that the concentration of vascular endothelial growth factor A (VEGF-A) had a moderate relationship with C-reactive protein (CRP), age, lipid profile parameters, systolic blood pressure, BMI, and physical activity. In the course of a large number of studies, an association exists between VEGF and glycemic profile in both healthy individuals and patients with diabetes mellitus [10]. **??**autero O. et al. show that the level of circulating VEGF is significantly higher, the severer ischemia manifestations are [11].

There is an assumption that biological age (BA), in contrast to the calendar age (CA), can serve as an indicator of vascular aging. Establishment of BA by anthropometric parameters according to the method by A. H. Horelkin and B. B. Pinkhasov is convenient to use since it does not require any specialized laboratory equipment [12].

When developing new and effective therapeutic strategies for improvement and prevention of "vascular aging" processes in cardiovascular disorders, it is essential to understand the cellular and functional changes that occur in the bloodstream during aging. The proposed factors that take into account the formation of cardiovascular risk (CVR) do not always allow classifying patients into risk groups of CVD development, which is why the search for cardiometabolic predictors that could influence the more reliable identification of patients at risk continues. In this connection, the objective of our study was an investigation of vascular aging markers in conjunction with metabolic parameters and CVR degree.

2 II.

3 Materials and Methods

This study included 298 patients. The age of the subjects was 40-69 years, median 44.9 years. Medical documentation (outpatient and inpatient patient histories) was analyzed to assess the presence of risk factors and calculate the total CVR on the SCORE scale.This became the basis for the distribution of patients into CVR groups: low and moderate (0-4% on the SCORE scale), high (5-9% on the SCORE scale) and very high (?10% on the SCORE scale) without clinical manifestations of CVD. According to the study protocol, patients were divided into groups according to the level of total cardiovascular risk according to SCORE: group I included patients (n = 101) with low CVR -33.9%; group (II) included patients (n = 125) with moderate risk -41.9%; group (III) included patients (n = 72) with high/very high risk -24.2%. Table 1 shows the distribution of patients according to the calculation of the total CVR on the SCORE scale. a) The inclusion criteria for the study were as follows 1) Age of men and women -40 to 69 years;

2) The presence of one or more of the following risk factors: essential hypertension of 1-2 degree, smoking, dyslipidemia, dysglycaemia, overweight or obesity; 3) The presence of signed informed patient consent to participate in the study.

4 The non-inclusion criteria for the study were

1) The presence of heart disease (clinically pronounced coronary artery disease, history of MI, coronary revascularization, chronic cardiac failure of blood circulation above functional class 2 according to NYHA), cerebral circulation disorders, atherosclerotic lesion of peripheral arteries; 2) Decompensated liver and kidney diseases with impaired function; 3) Oncological diseases; 4) Rheumatic diseases; 5) Allergic and autoimmune diseases; 6) Diabetes mellitus; 7) Pregnancy; 8) Use of lipid-lowering drugs; 9) Use of medicinal products affecting the state of the hemostas is system and blood rheology within 6 months prior to the inclusion in the study; 10) Essential hypertension of the third degree according to the criteria recommended by the European Society of Hypertension (ESH, 2016) [13].

Study protocol and materials pertinent to the study were reviewed and approved by the ethics committee of the Sociological Association of Ukraine and after obtaining informed verbal consent from the patients according to the Helsinki Declaration II.

Determination of lipid and carbohydrate metabolism parameters was carried out according to the generally accepted procedure, CRP concentration was measured using a test system (Best Diagnostics, Ukraine).Tumor necrosis factor-? (TNF-?) was measured using a test system (Vector-Best JSC, Russia), serum insulin was measured using a test system (DRG Instruments GmbH, Germany) under fasting conditions via enzyme-linked immunoassay (ELISA) on a semi-automatic micro plate analyzer Immuno Chem -2100 (High Technology, Inc., USA). Biochemical marker of endothelial dysfunction, VEGF-A, was tested by enzyme-linked immunoassay on photometer-analyzer Huma Reader using a set of reagents from IBL International GmbH, Germany.

DNA for measurement of the relative length of telomeres was isolated from buccal epithelium and peripheral blood leukocytes using DNA-sorb-AM and DNA-sorb-B reagents (Amplisense, Russia), respectively. A fluorometric method was applied to measure DNA concentration in the samples using via Qubit 3.0 fluorometer (Life Technologies, USA) and the Qubit dsDNA HS Assay Kits (Life Technologies, USA). DNA samples were diluted at a concentration of 2-4 ng/?l and stored until amplification at -20 ° C.

PCR with real-time detection of fluorescence was used to measure the relative length of telomeres according to the protocol described by Cawthon R. M., 2002 [14].The following primers produced by Invitrogen (Thermo

Fisher Scientific) were used to amplify telomeric sequences:? Tel1 GGTTTTTGAGGGTGAGGGTGAGGGTGAGGGTGA GGGT; ? Tel2 TCCCGACTATCCCTATCCCTATCCCTATCCCTATC CCTA.

The following primers produced by Invitrogen (Thermo Fisher Scientific) served for amplification of the reference single-copy gene 36B4 (ribosomal phosphor protein):? 36B4u CAGCAAGTGGGAAGGTGTAATCC; ? 36B4d CCCATTCTATCATCAACGGGTACAA.

For each of the primer systems, we prepared two reaction mixtures per the required number of samples using the iQ SYBR Green Supermix master mix (BioRad Laboratories, USA). We made the reaction mixture immediately before use. 11?l of the reaction mixture and four ?l of DNA were added to strip PCR tubes. Series of dilutions of the reference DNA sample (dilution range from 0.28 to 7.5 ng/?l) were performed separately for telomeric sequences and a single-copy gene to plot the calibration curves for estimation of the average telomere length. We examined each sample in 3 technical replicates.

Amplifications were performed using the CFX96 Touch detection system (BioRad Laboratories, USA) according to separate protocols for the target and reference gene. PCR protocol for telomeric sequences: DNA pre-denaturation -95 ° C, 5 minutes, followed by 35 cycles at 95 ° C, 20 s., 54 ° C, 2 minutes; for singlecopy gene 36B: DNA pre-denaturation -95 ° C, 5 min., and then 35 cycles at 95 ° C, 20 s., 58 ° C, 1 min.

The obtained results were processed using CFX96 Touch Software V.3 (BioRad Laboratories, USA) to generate telomeric signal curves (T) or a single-copy reference gene signal (S), evaluate the amplification reaction efficacy and determine Ct (the number of cycles required to achieve thethreshold level of fluorescence). To estimate the relative length of telomeres (T/S), the difference of threshold cycles for telomeric (Ct tel) and reference (Ct ref) sequences was calculated using the formula Î?”Ct x = Ct tel -Ct ref . Besides, we calculated the average Î?”Ct k for all reference and blank samples. We carried out normalization of the T/S value for each of the analyzed samples relative to the average Î?”Ct k value using the formula:T S = ?2 ?(Ct x ??Ct k) ? = [2 ???Ct].

Biological age was determined according to the procedure by A. H. Horelkin and B. B. Pinkhasov [12]. First, we calculated the aging rate factor, and then the biological age was calculated based on it. The formula for estimating the aging rate factor (ARF): ;?????? ?? = ???? ×???? ????×?? 2 ×(

where ARF m and ARF f are aging rate factors for men and women, respectively, WC -waist circumference, BWbody weight, HC-hip circumference, H-body height, AD m and AD f -the difference between the calendar age and the age according to ontogenetic standard for men and women, respectively. The ontogenetic standard is the age by which development and formation of the structure and functions of all systems of the human body are completed in the process of ontogenesis (individual human development). This age is 21 years old for men and 18 years old for women.

When ARF is 0.95 inclusive to 1.05 inclusive, the rate of aging is deemed compliant with the standard; when ARF is less than 0.95, the aging is delayed, when ARF is more than 1.05, the aging is accelerated. Formulas for determining biological age:???? ?? = ?????? ?? × (???????????????????????????????? ? 21) + 21; ???? ð ??”ð ??” = ?????? ð ??”ð ??” × (???????????????????????????????? ? 18) + 18;

where BA m and BA f is biological age for males and females, respectively.

All statistical analyses were performed using SPSS software (statistical package for social science), version 19.0. Analysis of the parameters studied by the normality of distribution was carried out using the Shapiro-Wilk test. We presented quantitative variables in the form of M ± m (M is the average value, m is its standard error), and described qualitative characters as the frequency of events (% of the normal number of observations). We used Student's t-test to determine the differences between dependent and independent samples. The rate of characters in the groups was compared using the ? 2 test. We carried out a correlation analysis using the Pearson test (r) and the Chad dock scale to determine the presence and nature of the F pathogenetic factors of different processes. Analysis of variance was used to establish the role of individual factors, and a logistic regression method was used to determine the likelihood of development of a cardiovascular event. Differences were deemed to be statistically significant at p <0.05.

III.

5 Results and Discussion

Comparison of the calendar and biological age showed that BA of the subjects was lower than the calendar age (CA) by 3.02 ± 0.01 years in the low CVR group, by 1.14 ± 0.02 years in the moderate CVR group, and was higher by 2.23 ± 0.01 years in the high/very high CVR group, which is evidence of the increasing rate of aging with increasing CVR.

When analyzing the comparative characteristics of parameters in the group of patients with low and moderate CVR, statistically significant differences were found in carbohydrate metabolism: glucose level 4.20 ± 0.01 mmol/l vs 6.23 ± 0.17 mmol/l (p = 0.049), insulin 14.23 ± 0.65 mU/l vs 16.42 ± 1.16 mU/l (p = 0.018), immune inflammation parameters: CRP 6.71 ± 1.02 mg/l vs 9.46 ± 0.41 mg/l (p = 0.026), TNF-? 6.90 ± 0.36 pg/ml vs 8.9 ± 0.47 pg/ml (p = 0.048) (Table 2). Significant differences between moderate and high/very high CVR groups in lipid metabolism parameters are noted: total cholesterol (TC) is 5.86 ± 0.13 mmol/l vs 7.24 ± 0.22 mmol/l (p = 0.000), triglycerides (TG) 2.25 ± 0.08 mmol/l vs 2.75 ± 0.11 mmol/l (p = 0.000), low-density lipoprotein cholesterol (LDL cholesterol) 3.62 ± 0.17 mmol/l vs 4.31 ± 0.27 mmol/l (p = 0.040) and very low density cholesterol (VLDL cholesterol) 0.87 ± 0.01 mmol/l vs 1.03 ± 0.05 mmol/l (p = 0.008); carbohydrate metabolism: blood glucose 6.25 ± 0.17 mmol/l vs 7.09 ± 0.27 mmol/l (p = 0.012), insulin 16.42 ± 1.16 mU/l vs

23.59 ± 2.62 mU/l (p = 0.018); immune inflammation: CRP 9.46 ± 0.41 mg/l vs 11.43 ± 0.59 mg/l (p = 0.027), TNF-? 8.90 ± 0.37 pg/ml vs 11.96 ± 0.95 pg/ml (p = 0.001) and endothelial dysfunction: VEGF-A1 422.82 ± 10.01 pg/ml vs 646.44 ± 58.11 pg/ml (p = 0.001) (Table **??**). Significant differences depending on CVR degree were found in telomere length among the groups of patients with moderate and high/very high CVR: 0.94 ± 0.03 vs 0.76 ± 0.05 (p = 0.027) in blood cells; 1.21 ± 0.05 vs 0.83 ± 0.07 (p = 0.045) in buccal epithelium (Table **??**).

6 Table 4: The presence of a relationship between the vascular aging markers and metabolic parameters in the group of low CVR patients

The correlation analysis showed a strong inverse correlation between HDL cholesterol and CRP in group I (r = -0.97; p = 0.002) and a moderate inverse correlation in group II (r = -0.33; p = 0.029) (Tables 4, 5). Zangana S.N. reported similar results, where CRP concentration positively correlated with cholesterol, TG and LDL levels, but inversely correlated with HDL level, and CRP level showed increase in individuals with arterial hypertension versus the healthy population [18]. During the study, we found a strong inverse correlation between HDL cholesterol and the length of telomeres in blood in the low CVR group (r = -0.90; p = 0.014), which indicates the effect of this parameter on the rate of biological aging. This correlation corresponds to the data by Mazidi, Mohsen, et al., where the mean HDL cholesterol concentrations increased significantly with increasing telomere length (p = 0.013), and the level of C-reactive protein significantly decreased with increasing telomere length (p <001) [15]. Strong inverse correlation in the low CWR group was observed between HDL cholesterol and insulin (r = -0.87; p = 0.024), HDL cholesterol and TG (r = -0.95; p = 0.004) (Table **??**). This is reflected in the studies by Sneha, S. et al., where HOMA-IR was higher among individuals with low HDL level (compared to normal HDL level), and the positive correlation of HOMA-IR and TG/HDL suggested that the TG/HDL ratio can be used as a marker of insulin resistance, as was also confirmed by Young, Kendra A., et al. [16,17] A reliable moderate direct correlation was found in group III between CRP and total cholesterol (r = 0.49; p = 0.022), VLDL cholesterol (r = 0.43; p = 0.048) (Table 6). Rathore, Vedika, et al. also found significant changes in the lipid profile levels and inflammatory markers in patients with acute myocardial infarction; they have established a strong positive correlation between CRP and total cholesterol, TG, LDL cholesterol and VLDL cholesterol, and significant negative correlation with HDL cholesterol, which can be a confirmation of preceding development of immune inflammation and lipid profile disorders [19]. The data of studies by McGarrah R. W., et al., also emphasize the interrelation between systemic inflammation and HDL cholesterol with clinical outcomes, consideration of which allows to improve the accuracy of clinical risk assessment [20]. VEGF-A1 as an indicator of immune inflammation is a factor associated with a subsequent increase in the CVR degree, as evidenced by a significant relationship between VEGF-A1 and VLDL cholesterol (r = 0.59; p = 0.004), as well as VEGF-A1 and shortening of telomere lengths (buccal epithelium) (r = 0.43; p = 0.044) in the high/very high CVR group (Table 6). Considering that 68% (n = 203) of the patients included in the study were immune resistant, we evaluated the telomere length depending on the serum insulin concentration. In patients with hyperinsulinemia> 30 mU/l, their length in the blood was 0.82 ± 0.13 vs 0.95 ± 0.03 at insulin levels <30 mU/l (p = 0.016). Similar changes occurred in the buccal epithelium: 0.80 ± 0.03 vs 1.10 ± 0.04 (p = 0.004) (Table 7). We determined the lower and upper margins of the confidence interval (CI) for interval estimates of the median. The sequence numbers of the sample values, which represented the lower (L) and the upper (U) margins, were determined using the formulas:?? = ?? 2 ? ??? 1??? × ??? 2 ?, ?? = 1 + ?? 2 + ??? 1??? × ??? 2 ?,

where n is the sample size, z 1-? is the value of the normal distribution for the selected confidence probability.

After calculating the sequence numbers of the lower and the upper CI margins, we determined their value in the sample. We used the L-th value of the formed variational series as the lower CI margin, and the U-th value as the upper CI margin.

Since the control group included 20 subjects, L = 6 is obtained for a confidence probability 95% z (1?) = 1.96. That is why the 95% CI for the parameter "telomere length of blood cells" was [1.38; 2.09]. By the obtained CI, an analysis of the frequency of occurrence of the normal and shortened telomeres of blood cells depending on CVR was carried out (? 2 = 3.076, p = 0.215) (Table 8). F 95% CI for the parameter "telomere length of buccal epithelium cells" was **??**1.45; 2.18]. Analysis of the frequency of occurrence of normal and shortened telomeres of the buccal epithelium cells depending on the CVR was carried out (? 2 = 0.547, p = 0.761) (Table **??**). According to the results of frequency analysis, we have revealed that the vast majority of the study patients who had shortened telomeres were the patients with moderate CVR (48.4 ± 4.4% in blood and 50.0 ± 4.4% in buccal epithelium) (Table 8, 9). Probably, already in the presence of moderate CVR in this patient category, timely diagnosis of the onset of vascular aging is necessary to prevent the development of CVR of higher degrees.

7 Table 9:

The frequency of occurrence of normal and shortened telomeres of buccal epithelium cells depending on CVR Due to the increase in CRP and insulin levels and the degree of CVR, according to our study, patients experience a significant shortening of telomere length. Shortening can be associated with the destruction of the structure of

telomere T-loop, which leads to cellular aging, increased oxidative stress and inflammation in the tissues (Morgan, R. G. et al.) [21].

Considering the results obtained, it can be assumed that the quality of control of the lipid spectrum and carbohydrate spectrum decreases in the high/very high CVR group, which leads to acceleration of immune inflammation and increase in the rate of vascular aging, which in turn leads to an increase in the number of cardiovascular complications, increased vascular aging rate.

IV.

8 Conclusion

1. Patients with cardiovascular risk (CVR) of high degrees compared with low and moderate CVR show a more pronounced impairment in the lipid and carbohydrate profile. This can be the cause of acceleration of vascular aging processes and require more stringent control of the lipid profile and glucose parameters to improve secondary prevention. 2. The relationship between CRP and shortening of telomere length in the buccal epithelium in the high/very high CVR group, as well as between CRP and lipid profile parameters in all CVR groups indicates the development of premature aging processes. For timely secondary prevention, it is advisable to measure CRP and TNF-? in individuals with high CVR degrees. 3. For reduction of the activity of vascular aging and primary prevention of cardiovascular diseases (CVDs), it is essential to consider markers of systemic inflammation (CRP, TNF-?) and to ensure good glycemic control not only via screening of fasting glucose but also using HOMA index as a more reliable indicator.

4. To identify groups of patients at increased risk of complications and accelerated biological aging, it is advisable to determine the biological age of individuals with high/very high CVR at a stage even preceding laboratory examinations. 5. Patients from a risk group in the presence of even moderate CVR show a significant decrease in telomere length, which can serve as an essential factor that indicates the onset of premature vascular aging in this patient category and requires early preventive interventions. [1]

1

	CVR on the SCORE scale					
Age, years	Low/moderate, n=101		High, n=125		Very high, n=72	
	Abs.	%	Abs.	%	Abs.	%
40-49	38	38.4±3.5%	44	35.2±4.3%	14	19.8±1.7%
50-59	51	49.5±5.0%	38	30.2±4.1%	17	23.5±5.0%
60-69	12	12.1±3.2%	43	34.6±4.2%	41	56.7±5.8%

Figure 1: Table 1 :

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2

Parameter	Low CVR group	Moderate CVR group	p-criterion
Lipid metabolism parameters			
Total cholesterol,mmol/l	5.68±0.10	5.86±0.13	0.931
Triglycerides,mmol/l	2.10±0.04	2.25±0.08	0.834
LDL cholesterol,mmol/l	3.19±0.013	3.62±0.17	0.854
VLDLcholesterol,mmol/l	0.76±0.02	0.87±0.01	0.784
HDL cholesterol,mmol/l	1.03±0.035	0.92±0.04	0.831
Carbohydrate metabolism parameters			
Glucose,mmol/l	4.20±0.013	6.23±0.17	0.049
Insulin,mU/l	14.23±0.65	16.42±1.16	0.018
Immune inflammation parameters			
CRP,mg/l	6.71±1.02	9.46±0.41	0.026
TNF-?,pg/ml	6.90±0.36	8.9±0.47	0.048
Endothelial dysfunction parameter			
VEGF-A1,pg/ml	319.94±66.47	422.82±10.01	0.461
Telomere length			
Blood	1.14±0.08	0.94±0.03	0.326
Buccal epithelium	1.30±0.02	1.21±0.05	0.235

Figure 2: Table 2 :

5

Insulin	p-value

Figure 3: Table 5 :

	TG	p-value
Insulin	0.84	0.035
	HDL cholesterol	
CRP	-0.97	0.002
Telomere length (blood)	-0.90	0.014
Telomere length(buccal epithelium)	-0.79	0.065
TG	-0.95	0.004
Insulin	-0.87	0.024

Figure 4:

6

	Total cholesterol	p-value
CRP	0.49	0.022
VLDL cholesterol	0.47	0.028
	VLDL cholesterol	
CRP	0.51	0.015
VEGF-A1	0.59	0.004
CRP	Telomere length (buccal epithelium)	
?RP	0.51	0.016
VEGF-A1	0.43	0.044

Figure 5: Table 6 :

7

Parameter	Insulin<30 mU/l, n=119	Insulin> 30 mU/l, n=179	p-value
Telomere length (blood)	0.95±0.03	0.82±0.13	p=0.016
Telomere length (buccal epithelium)	1.10±0.04	0.80±0.03	p=0.004

Figure 6: Table 7 :

8

Figure 7: Table 8 :

.1 Abbreviations

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