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RELATIVE LEUKOCYTE TELOMERE LENGTH IN PATIENTS WITH CHRONIC ALCOHOL ADDICTION DEPENDING ON CLINICAL AND ANAMNESTIC CHARACTERISTICS

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The studies conducted on human cell lines demonstrated that even moderate alcohol consumption caused the shortening of telomeres – structures that play a key role in of cellular aging. Nevertheless, published data on the effect of chronic alcohol intake on the changes in the relative leukocyte telomere length (LTL) in humans remain ambiguous. Such ambiguity may be attributed to the differences in the clinical symptoms of individuals with alcohol dependence. In this regard, the present study aimed to test for the hypothesis, which suggests the association of shorter telomeres with manifesting chronic alcoholism and to identify clinical and anamnestic characteristics associated with individual variance in relative telomere length in subjects with alcohol dependence. LTL assessment has been carried out via real-time PCR in patients diagnosed with alcohol dependence syndrome (ICD-10) (N = 272) and in control group (N = 254). Linear regression analysis demonstrated statistically significant effect of age in the total sample (βstand = -0.153, P = 0.009) and in men (βstand = -0.143, P = 0.026) on variance in LTL. Moreover, age-dependent telomeres shortening was characteristic only for patients’ group (βstand = -0.217, P = 0.017). The inclusion of clinical and anamnestic characteristics in the model resulted in a significant negative effect of age at onset of withdrawal syndrome on LTL (βstand = -0.343, P=0.001). The findings obtained are congruent with the data on the toxic effect of acetaldehyde and increased allostatic load accompanied by prolonged alcohol consumption, and confirm the presence of a compensatory effect in the cells, which is associated with regulated expression of genes responsible for maintaining telomere length.

Keywords: alcohol addiction, telomeres, cell aging, allostatic load, biomarkers, clinical and anamnestic characteristics

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Introduction. Telomeres are heterochromatin structures located at the ends of the chromosomes and consisting of 5’-TTAGGG-3’tandem repeats. These structures protect chromosomal ends from fusion and degradation, therefore, maintaining their integrity and stability, and play a key role in cellular aging [6]. Recent studies have demonstrated the influence of several environmental factors, including stress of various nature, on the modified telomeres length in humans in dynamics. However, the causal relationships between the effect of adverse environment and changes in telomere length are still incompletely understood. Together with individual variations in the number of telomeric repeats caused by age [11], sex and ethnic differences [18], unfavorable environment [10], chronic alcohol intake results in severe stress in biological systems, causing excessive allostatic load [19].

During the last decades a candidate gene approach [1, 2, 5, 9], genome-wide association studies (GWAS) [8], assessment of epigenetic changes [3, 13] have been used for the study of alcohol dependence and antisocial behavior in order to identify genetic predictors. Together with mentioned approaches, in recent years the assessment of the relative telomere length in peripheral tissues of individuals with various mental disorders became of high relevance [15, 17, 19]. The studies conducted on human cell lines demonstrated that even moderate alcohol treatment for one week resulted in telomeres shortening in different cell types [6]. A similar effect was observed in the case of cells’ exposure to acetaldehyde (an intermediate metabolite of ethanol) at the same concentration, which confirmed a toxic effect of this metabolite on cells, thus causing a premature “cell aging”. Other authors also indicated the changes in the expression of genes responsible for maintained telomere length (including shelterin complex genes), depending on the duration of ethanol exposure to human embryonic stem cells and its concentration [12]. Nevertheless, published data on the effect of chronic alcohol intake on changes in the relative leukocyte telomere length (LTL) remain ambiguous. In particular, both telomeres shortening in addicted individuals [14, 17] and the absence of such association have been reported [15, 20]. Such ambiguity may be attributed to the differences in the severity of clinical symptoms (in particular, the presence of acute alcoholic psychosis, delirium, etc.) in individuals with alcohol dependence. Despite the LTL studies, which assessed the effect of both alcohol addiction and comorbid addiction with other psychoactive substances [19], no studies evaluating the role of clinical and

anamnestic parameters on LTL in subjects with alcohol dependence have been carried out to date.

Considering the abovementioned data, the present study aimed to test for the hypothesis, which suggests the association of shorter telomeres with manifesting chronic alcoholism, form the one hand. On the other hand, it was suggested to identify clinical and anamnestic characteristics associated with individual variance in relative telomere length in subjects with alcohol dependence.

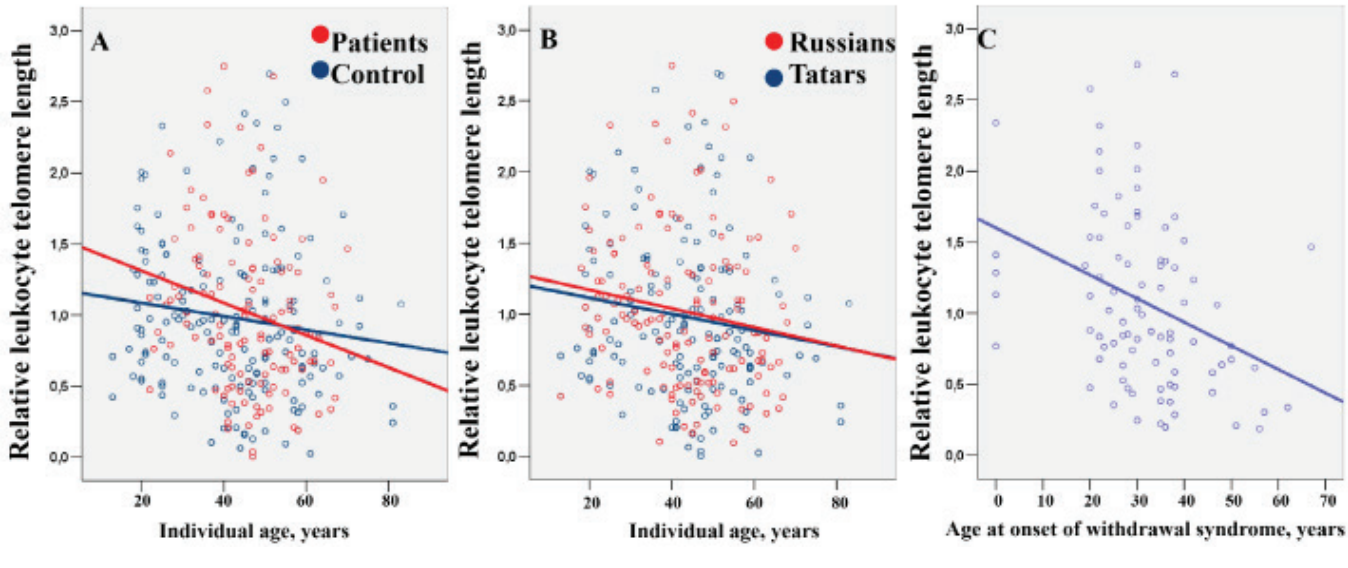
Materials and methods. The study sample included patients diagnosed with “alcohol dependence syndrome” (ICD-10) (N = 272, 12% women) of different ethnicity (134 Russians, 112 Tatars, 26 subjects of mixed ethnicity). Mean age of patients was 45.54 ± 11.08 years. Control group (N = 254, 12% women) consisted of mentally healthy individuals without individual or family history of psychiatric disorders. Control group corresponded to the sample of patients by age (mean age 42.08 ± 15.68 years), sex and ethnic content (150 Russians, 107 Tatars and 15 individuals of mixed ethnicity). All the enrolled subjects signed an informed consent after they were acquainted with all the procedures. This study was approved by the local Bioethical Committee at the Institute of Biochemistry and Genetics (UFRC RAS).

A collection of biological material (peripheral blood) was conducted in 2009-2010 followed by DNA extraction via phenol-chloroform technique. LTL quantitative assessment was carried out via real-time PCR on “CFX96” Analyzer (BioRad, USA) using fluorescent intercalating dye IQ SYBR Green Supermix (BioRad, USA). PCR mix contained a pair of primers designed to telomeric region (T) and to single-copy beta-globin gene (*HGB*) as a conservative one (S) [7]. For each sample, which has been analyzed in triplicate, a mean value of cycle threshold (Ct) has been calculated for the conservative gene and for the telomeric region. The samples, which demonstrated differences in Ct values between the triplicates for more than 30%, have been excluded from the analysis. Pool DNA was used as a control sample in each PCR run (reproducibility was above 98%).

LTL for each individual was calculated based on the method based on the formula $2^{-\Delta\Delta Ct}$ described previously [10]. For this purpose a difference in the cycle thresholds for the telomeric and control PCR and a relative telomere length in a genome (T/S) was assessed according to the formula $T/S=2^{-\Delta\Delta Ct}$, where $\Delta\Delta Ct = (Ct_T(sample) – Ct_T(poolDNA)) - (Ct_S(sample) – Ct_S(poolDNA))$. A relative leukocyte telomere length in a genome (T/S) is proportional to $2^{-\Delta\Delta Ct}$ and a telomere length in the analyzed sample.

Statistical analysis included a series of multiple regression analyses, which included LTL as dependent variable, while status (being patient or mentally healthy subject), individual age, sex and ethnicity, age at onset of withdrawal syndrome and age at onset of first alcohol probe, family history of psychopathologies, number of hospitalizations in anamnesis and the number of premorbide traumatic brain injuries were included as independent predictors. In the case of statistically significant effect of a predictor we reported both regression coefficient (β) and standardized regression coefficient (β_{stand}). A correlation analysis was conducted via Spearman's rank correlation coefficient. Statistical analysis and data visualization was carried out with R v.4.1.2.

Results and discussion. Within the framework of the present study in order to test for the hypothesis on the association of LTL with alcohol dependence we conducted a series of linear regression analyses with sex and age inclusion as covariates. Statistically significant effect of age was determined in the total sample (β = -0.006, β_{stand} = -0.153, P = 0.009) and in men (β = -0.005, β_{stand} = -0.143, P = 0.026) on LTL variance (Table 1). Due to a small sample size of women, statistical analysis in women separately has not been conducted. A correlation analysis also demonstrated a negative correlation between LTL and age of individual (r= -0.178, P < 0.01). As a result of similar analyses performed in patients and control groups separately we revealed a statistically significant effect of age on telomeres shortening only in the group of addicted individuals (β = -0.011, β_{stand} = -0.217, P = 0.017), whereas a trend for a negative link between these two parameters was obtained for the control group (β = -0.005, β_{stand} = -0.133, P = 0.086). While dividing sample based on ethnic origin, we observed a trend for age-related telomeres shortening both in Russians (β = -0.007, P = 0.056) and in Tatars (β = -0.006, P = 0.084), which indicates the absence of significant effect of ethnicity on LTL decrease. Therefore, more rapid and statistically significant age-related decline in LTL is characteristic for patients with alcohol dependence compared to mentally healthy subjects regardless on ethnic origin (Fig., *a*). The



Dependence of relative leukocyte telomere length on age in a group of patients with alcohol dependence and control group (a), in individuals of different ethnic origin (b), on age at onset of withdrawal syndrome in patients with alcohol addiction (c).

data obtained are congruent with previously published findings on LTL drop in both mentally impaired individuals [11] and control ones [10], thus indicating an increased allostatic load.

At the same time, suggested hypothesis on a relation of shortened telomeres with a negative systematic organism exposure to ethanol has not been confirmed, since no statistically significant changes in LTL were obtained between the patients with alcohol addiction and the control group in the total sample (β = 0.024, P = 0.703) and in men (β = 0.010, P = 0.888) (Table 1). Since a relative decrease in telomere length was reported in Europeans compared to individuals of other ethnic groups [18], we conducted the analysis in Russians and Tatars separately. Nevertheless, a stratified analysis also failed to demonstrate a link between LTL and the presence or absence of alcohol addiction both in Russians (β = 0.045, P = 0.634) and Tatars (β = 0.032, P = 0.739) (Fig., *b*).

To date, no systematic meta-analysis has been published that makes it possible to make unambiguous conclusion on the link between telomere length and the presence of alcohol dependence. Nevertheless, there is evidence of the association of excessive alcohol consumption in mid-life with telomere shortening in elderly [17]. However, in the present study we failed to demonstrate differences in LTL between individuals with alcohol dependence and healthy controls. One of the possible causes may be attributed to individual differences in the activity of acetaldehyde dehydrogenase (ALDH2) – enzyme, which is responsible for acetaldehyde catalysis, and, consequently, for the accumulation of toxic products of ethanol degradation and their effects on cells. In particular, one of the studies demonstrated a negative association between LTL and enhanced alcohol consumption, which was prominent only in the case of a low-active form of ALDH2 related to the presence of a mutant allele (rs2074356 C/T or T/T genotypes) in the encoded gene [16]. Moreover, the highest effect of such association was more evident with age. At the same time, the average level of alcohol consumption, on the contrary, was associated with increased LTL; however, such association was characteristic only for carriers of high-active rs2074356 C/C genotype in the *ALDH2* gene [16]. In addition, telomere shortening was observed in patients with alcohol dependence only in the case of genetically determined high-active form of alcohol dehydrogenase (ADH), an enzyme involved in the ethanol conversion to acetaldehyde [14]. Thus, published data indicate a negative relationship between telomere length and the exposure to high doses of alcohol only in the case of toxic effects of ethanol degradation products (i.e., a low-active form of ALDH2 and a high-active form of ADH). Similarly to our findings on the association of LTL with alcohol consumption, several foreign researchers also demonstrated the absence of such link [20]. It should be noted that recent large-scale study, which evaluated the effect of the summarized

Table 1

Multiple regression analysis demonstrating the effect of several predictors and clinical and anamnestic characteristics on individual variance in LTL in the total sample, in men and patients with alcohol dependence

Group	Predictor	Reference group	Model 1		Model 2		Model 3		Model 4	
			β_{stand}	p-value	β_{stand}	p-value	β_{stand}	p-value	β_{stand}	p-value
Total sample	Intercept	-	1.266	<0.001	0.976	<0.001	1.202	<0.001	1.408	<0.001
	Status	control	-	-	0.022	0.703	-	-	0.054	0.353
	Sex	men	-	-	-	-	-0.120	**0.033**	-0.103	0.080
	Age	-	-0.153	**0.009**	-	-	-	-	-0.144	**0.016**
	P-value of model		**0.009**		0.703		**0.033**		**0.013**	
	Corrected r^2		0.023		<0.001		0.014		0.037	
Men	Intercept	-	1.263	<0.001	1.010	<0.001	1.202	<0.001		
	Status	control	-	-	0.009	0.888	0.042	0.512		
	Age	-	-0.143	**0.026**	-	-	-0.149	**0.022**		
	P-value of model		**0.026**		0.888		0.068			
	Corrected r^2		0.020		<0.001		0.022			
Patients with alcohol addiction	Intercept	-	1.601	<0.001	1.082	<0.001	1.713	<0.001	1.603	<0.001
	Sex	men	-	-	-	-	-	-	-0.052	0.659
	Age	-	-	-	-	-	-	-	0.060	0.747
	Ethnicity	Tatars	-	-	-	-	-	-	0.022	0.849
	Family history	no	-	-	-	-	-	-	0.051	0.659
	Age alcohol start	-	-	-	-	-	-	-	0.065	0.729
	Age withdrawal	-	-0.343	**0.001**	-	-	-0.361	**0.001**	-0.408	**0.039**
	Hospitalization	0	-	-	-0.151	0.129	-0.211	**0.047**	-0.275	**0.046**
	TBI	0	-	-	-	-	-	-	-0.008	0.947
	P-value of model		**0.001**		0.129		**0.001**		0.172	
	Corrected r^2		0.117		0.023		0.150		0.156	

Note. Corrected r^2 – corrected coefficient of determination; βstand – standardized regression coefficient; family history – family history of psychopathologies; age alcohol start – age at the first alcohol probe; age withdrawal – age at onset of withdrawal syndrome; hospitalization – number of hospitalizations in anamnesis; TBI – number of premorbide traumatic brain injuries. Statistically significant differences are marked in bold.

parameter of a healthy lifestyle (including moderate alcohol consumption) in more than 420 thousand individuals from the UK Biobank demonstrated only its insignificant effect (less than 0.2%) on individual variance in LTL [4]. Moreover, the authors failed to determine association of LTL with any of examined diseases. At the cellular level, the absence of significant long-term negative effects of ethanol on human cells has been also shown, which is explained by regulated expression of the genes associated with maintaining telomeres length in cells. In particular, in the case of short-term (3 days) exposure to ethanol of human embryonic stem cells, a decrease in the expression of six genes encoding shelterin complex subunits was observed, while longer exposure (7-14 days) was related to restored expression of these genes and the absence of ethanol-dependent telomere shortening [12].

In order to test the second hypothesis we performed the assessment of relation of clinical and anamnestic characteristics (age at onset of withdrawal syndrome and first probe of alcohol, family history of psychopathologies, number of hospitalizations in anamnesis and premorbide traumatic brain injuries) to individual differences in LTL in addicted patients. The data on the examined clinical and anamnestic characteristics in individuals with alcohol dependence is shown in Table 2. While including all characteristics in the regression model, a statistically significant effect o of age at onset of withdrawal syndrome (β = -0.017, β_{stand} = -0.343, P=0.001) n LTL was observed (Table 1, Fig., *c*). At the same time, sex (β = -0.083, P = 0.659), ethnicity (β = 0.027, P = 0.849), positive family history of psychopathologies (β = 0.065, P = 0.659), age at first probe of alcohol (β = 0.004, P = 0.729), presence of premorbide traumatic brain injuries (β = -0.002, P=0.947), number of hospitalizations in anamnesis (β = -0.027, P=0.129) demonstrated insignificant effect of LTL among patients (Table 1). A correlation analysis revealed a positive relation between patient age and age at onset of withdrawal syndrome (r = 0.603, P < 0.001) and the number of hospitalizations (r = 0.274, P = 0.006), and between age at first probe of alcohol and age at onset of withdrawal syndrome (r = 0.749, P < 0.001). At the same time, no correlation was observed between age at onset of withdrawal syndrome and the number of hospitalizations (r = -0.160, P = 0.148).

Our results on rapid decrease in LTL in patients with alcohol addiction may be related to with the toxic effect of acetaldehyde [16], which causes accelerated cellular aging of the body. In turn, revealed differentiation in telomere length depending on the age at onset of acute alcoholic psychosis (within the withdrawal syndrome) is probably caused by a correlation between the age of manifestation of withdrawal syndrome and individual age. This dependence is logically consistent with the duration of a negative effect of ethanol exposure on the organism. Despite the suggested hypothesis on the relationship of clinical and anamnestic characteristics with variations in telomere length between individuals with alcohol dependence, we failed to identify statistically significant relations with respect to the number of premorbide traumatic brain injuries and the number of hospitalizations, family burden with psychopathologies, and earlier age of the first probe of alcohol. To date, there are no published data on the association of telomere length with the severity of clinical symptoms in alcohol dependence. However, one of the studies reporting a trend for diminished telomere length individuals with chronic alcohol addiction with comorbid cocaine abuse has to be mentioned [19]. Moreover, as part of the assessment of the enhanced allostatic load, the authors demonstrated that chronic alcohol intake, together with the duration of cocaine addiction, older age and reduced LTL predicted decreased cognitive functioning. Another study, similar to our negative results, reported no association of LTL with even prolonged exposure to severe psychoactive substances (methamphetamine), following psychosis and withdrawal syndrome [15]. Accordingly, the data obtained by our group and published findings do not confirm that individual changes in LTL are attributed to comorbid use of other psychoactive substances, as well as to clinical and anamnestic characteristics.

Table 2

Mean LTL level depending on examined clinical and anamnestic characteristics in patients with alcohol addiction

Parameter	Mean±SD*	Parameter	Mean±SD*
Sex		Number of traumatic brain injuries	
Men (N = 239)	1.02±0.60	0	1.01±0.59
Women (N = 33)	0.89±0.48	1	0.99±0.57
		≥2	1.03±0.69
Ethnicity			
Russians (N = 150)	1.04±0.53	Age	45.54±11.08
Tatars (N = 107)	0.99±0.62		
Family history of psychopathology		Age of first alcohol probe	30.09±11.45
yes (N = 106)	1.16±0.63		
no (N = 166)	0.96±0.53		
Number of hospitalizations		Age at onset of withdrawal syndrome	31.40±12.68
1	1.28±0.48		
2	0.83±0.51		
≥3	0.91±0.66		

*Mean ± standard deviation. For age-related quantitative variables (individual age, age of first alcohol probe, age at onset of withdrawal syndrome) the values are reported for the variable instead of LTL mean

Discussion. Within the framework of the present study an attempt to associate individual variance in the relative leukocyte telomere length to clinical and anamnestic characteristics of patients diagnosed with alcohol dependence syndrome has been carried out for the first time. As a result of the study of various characteristics we detected statistically significant negative effect of age of onset of withdrawal syndrome on LTL, which is attributed to a positive correlation of this parameter with individual age. Moreover, congruent with published data on age-dependent telomere shortening, we demonstrated a rapid and statistically significant decline in LTL with age in subjects with alcohol addiction regardless ethnic origin. Determined relation is consistent with the suggestions on a toxic effect of acetaldehyde and enhanced allostatic load related to the duration of alcohol consumption. It should be mentioned that the findings obtained failed to demonstrate telomeres shortening in addicted individuals compared to control group, which has been previously reported in other ethnic groups, and is congruent to the presence of a compensatory effect in the cells related to regulated expression of the genes involved in maintaining telo-

meres length. Despite the association of the age at onset of withdrawal syndrome with telomere shortening in patients, we failed to confirm suggested hypothesis on a relation of other clinical and anamnestic characteristics with LTL variance. Our findings evidence in insignificant effect of such clinical and anamnestic parameters as enhanced number of premorbide traumatic brain injuries, family history of psychopathologies, and reduced age at first probe of alcohol on accelerated cellular aging of the organism.

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