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ORIGINAL ARTICLE

RUSS-AGE study: Markers of carbohydrate metabolism and their time course in different age groups of a healthy population of the Russian Federation

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Abstract

Background. One of the important tasks of modern science is to search for key biomarkers of aging of various body systems. Parameters of carbohydrate metabolism play an essential role in maintaining vital activity. The prevalence of carbohydrate metabolism disorders increases with age, but the time course of changes in individual markers remains poorly understood. Therefore, it is important to investigate the patterns of changes in carbohydrate metabolism markers in different age groups among healthy participants, which is the objective of the RUSS-AGE study.

Aim. To evaluate changes in carbohydrate status markers (adiponectin, leptin, glucose, glycated hemoglobin, insulin, and carboxymethyllysine – CML) in different age groups of a healthy Russian population.

Materials and methods. The study was conducted at the Pirogov Russian National Research Medical University in collaboration with the Moscow City Outpatient Clinic No. 220. The study group included subjects 18 years of age and older who signed an informed consent form; the exclusion criteria were current acute disease, exacerbation of a chronic disease, surgical intervention within the last month, and moderate to severe chronic age-associated diseases. Blood samples were taken to measure aging markers: glucose (enzymatic ultraviolet method), insulin (chemiluminescent enzyme immunoassay), glycated hemoglobin (calorimetric method), CML, adiponectin, and leptin (enzyme immunoassay). The study was approved by the local ethics committee (Minutes No. 59 dated 13.09.2022). Statistical analysis was carried out using the R programming language version 4.4.0. The significance threshold for the *p*-value values given in the article is 0.05.

Results. The study included 711 participants, which were divided into eight age groups. According to the intergroup comparison, a statistically significant direct relationship of age with adiponectin ($p<0.001$), glucose ($p<0.001$), and glycated hemoglobin ($p<0.001$) was found. No significant correlation with age was found for leptin ($p=0.116$), insulin ($p=0.078$), and CML ($p=0.506$). After conducting a statistical analysis using linear regression to assess the dependence of variables on age, it was found that only adiponectin, glucose, and glycated hemoglobin significantly increase with age ($p<0.001$).

Conclusion. The study showed a significant increase in adiponectin, glucose, and glycated hemoglobin, while leptin, insulin and CML had no significant correlation with age.

Keywords: aging, carbohydrate metabolism, glucose, insulin, glycated hemoglobin, carboxymethyllysine, adiponectin, leptin

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ОРИГИНАЛЬНАЯ СТАТЬЯ

Исследование RUSS-AGE: маркеры углеводного обмена и их динамика в разных возрастных группах здоровой популяции РФ

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Аннотация

Обоснование. Одной из важных задач современной науки является поиск ключевых биомаркеров старения различных систем организма. Параметры углеводного обмена играют важную роль в поддержании жизнедеятельности. С возрастом распространенность нарушений углеводного обмена увеличивается, однако динамика изменений отдельных маркеров остается недостаточно изученной. В связи с этим актуально исследовать закономерности изменений маркеров углеводного обмена в различных возрастных группах среди здоровых участников, что и является целью исследования RUSS-AGE.

Цель. Оценить изменения маркеров углеводного статуса (адипонектина, лептина, глюкозы, гликированного гемоглобина, инсулина и карбоксиметиллизина – КМЛ) в разных возрастных группах здоровой российской популяции.

Материалы и методы. Исследование выполнено на базе ОСП РГНКЦ ФГАОУ ВО «РНИМУ им. Н.И. Пирогова» совместно с ГБУЗ «Городская поликлиника №220» г. Москвы. В исследуемую группу включались лица от 18 лет, которые подписывали форму информированного согласия; критериями исключения послужили наличие острого заболевания, обострение хронического заболевания или хирургического вмешательства в течение последнего месяца, хронические возраст-ассоциированные заболевания умеренной и тяжелой степени выраженности. Совершен забор образцов крови с дальнейшей оценкой маркеров старения: глюкоза (ферментативный ультрафиолетовый метод), инсулин (хемилюминесцентный иммуноферментный анализ), гликированный гемоглобин (калориметрический метод), КМЛ, адипонектин, лептин – иммуноферментный анализ. Исследование одобрено локальным этическим комитетом (протокол №59 от 13.09.2022). Статистический анализ проводился с помощью языка программирования R версии 4.4.0. Порог значимости для приводимых в статье значений *p*-value равен 0,05.

Результаты. В исследование включены 711 участников, которые распределены на 8 возрастных групп. По данным межгруппового сравнения выявлена статистически значимая прямая связь возраста с адипонектином ($p<0,001$), глюкозой ($p<0,001$) и гликированным гемоглобином ($p<0,001$). Значимая корреляция с возрастом не выявлена у лептина ($p=0,116$), инсулина ($p=0,078$) и КМЛ ($p=0,506$). После проведения статистического анализа методом построения линейных регрессий для оценки зависимости переменных от возраста установлено, что только адипонектин, глюкоза и гликированный гемоглобин значимо повышаются с возрастом ($p<0,001$).

Заключение. В ходе исследования удалось выявить значимое повышение адипонектина, глюкозы и гликированного гемоглобина, при этом у лептина, инсулина и КМЛ значимая корреляция с возрастом утеряна.

Ключевые слова: старение, углеводный обмен, глюкоза, инсулин, гликированный гемоглобин, карбоксиметиллизин, адипонектин, лептин

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Introduction

Due to an increase in life expectancy, the population structure has significantly changed. While in 2015, the number of people older than 65 was 617 million (8.5% of the total population), by 2050, it is expected to increase to 1.6 billion people, approximately 17% of the total population [1]. For this reason, ensuring healthy and active longevity for a growing number of older people is becoming a critical issue for modern society.

Although the risk of various diseases increases significantly with age, the health status of older people can vary significantly, showing that chronological age is not always an accurate indicator of the changes in the body and does not consider the actual decrease in its biological functions. There-fore, it is imperative to determine the biological age based on the analysis of several biomarkers that reflect the actual state of the organism.

During aging, carbohydrate metabolism changes occur, increasing the body's susceptibility to var-ious pathological conditions, including cardiovascular diseases and premature mortality [1]. In addi-tion, neurodegenerative disorders such as Alzheimer's and Parkinson's diseases are associated with impaired carbohydrate metabolism [2].

Due to the multifactorial effect of carbohydrate metabolism on the state of the body, the study of its biomarkers is necessary to predict the rate of aging and the risk of age-associated diseases.

Changes in glucose metabolism increase insulin secretion, leading to significant cellular stress, mitochondrial dysfunction, and increased free radical production [1, 2]. Hyperinsulinemia and asso-ciated insulin resistance are also important risk factors for type 2 diabetes mellitus (T2DM) and car-diovascular diseases. Elevated insulin concentrations have been shown in mouse models and humans to convert the phenotype of hepatocytes, adipocytes, and neurons to that of senescent cells [2]. Thus, insulin may play a significant role in developing age-related diseases and accelerating aging. Given the direct

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association of glycated hemoglobin (HbA1c) with glucose levels, it is also a predictor of many age-associated diseases. Also, some pathways for the production of carboxymethyllysine (CML), a glycation end-product, require the involvement of glucose [3]. The role of CML in aging and the development of age-associated diseases is a subject of scientific debate. The connection be-tween carbohydrate metabolism and adipose tissue is well-known, and age-related changes in adipo-cytes affect the synthesis and secretion of adipokines. One of them is adiponectin, which significant-ly influences metabolic processes and the general condition of the body [2]. It has been shown to in-crease insulin sensitivity, prevent type 2 diabetes mellitus, have a beneficial effect on the lipid pro-file, and have an anti-atherosclerotic effect [4, 5]. All of the above indicate the role of adipokine in aging, so studying trends in its changes is of great importance.

Another adipokine is leptin, which, in addition to peripheral activity, can pass through the blood-brain barrier and affect the structures of the central nervous system. In this way, it modulates eating behavior, energy expenditure, fat and glucose metabolism, and cardiovascular tone, including blood pressure and sympathetic nervous system activity [6]. Since many of these processes are extremely important for the body, leptin resistance can increase the risk of metabolic diseases, including obesi-ty, type 2 diabetes mellitus, and hypertension [6].

Therefore, carbohydrate metabolism and adipose tissue disorders lead to accelerated aging and re-duced life expectancy. In addition, age is the strongest known risk factor for carbohydrate metabo-lism disorders [1]. That is why analyzing the trends of these biomarkers during healthy aging will improve the understanding of the mechanisms of age-related changes.

Materials and methods

A cross-sectional cohort study was conducted from 2022 to 2024 as part of the collaboration be-tween a Separate structural division, the "Russian Gerontological Scientific and Clinical Center" of the Pirogov Russian National Research Medical University, and the Moscow City Outpatient Clinic No. 220.

Inclusion criteria:

1) a signed informed consent form;

2) age 18 years and older at the time of enrollment in the study.

Non-inclusion criteria:

1) presence of an acute disease, exacerbation of a chronic disease, or surgical intervention within the last month;

2) moderate or severe chronic age-associated diseases.

Blood samples were taken from participants to measure aging markers: glucose (enzymatic UV method), insulin (chemiluminescent enzyme immunoassay), HbA1c (calorimetric method), CML, adiponectin, and leptin (enzyme immunoassay).

The study was approved by the local ethics committee (Minutes No.59 dated 13.09.2022).

Statistical analysis was carried out using the R programming language version 4.4.0. In the first stage, the data were analyzed using descriptive statistics methods. The Shapiro-Wilk test was used to check the samples for deviations from the normal distribution. The numerical variables had a non-normal distribution and were described as follows: the number of non-missing values (N), the medi-an (Me), and the values of the 1st and 3rd quartiles (Q1; Q3). The Mann-Whitney test for two groups and the Kraskell-Wallis test for more than two groups were used to compare the groups. Categorical variables were described using absolute and relative numbers of participants. For comparison, the $\chi 2$ test and Fisher's exact test were used.

The significance threshold for the p-value values given in the article is 0.05.

To assess the relationship of laboratory markers with age, the graphical presentation of the results of linear regression estimation was used to construct a curve of the relationship of variables. If p-value <0.05 for the biomarker assay, then the biomarker changes with age. The upward direction of the line indicates a positive association of the marker with age, and the downward direction of the trend line indicates a negative association.

Results

The study included 711 participants, which were divided into eight age groups. The general char-acteristics of the study group are provided in Table 1.

An intergroup comparison was performed to assess the trends of carbohydrate metabolism mark-ers; the results are presented in Table 2.

The intergroup comparison showed the following results: the median values of glucose, HbA1c, and insulin in all age groups are within the reference values. Due to the low use in clinical practice, there are no reference values for adiponectin, leptin, and CML. According to the intergroup comparison, a statistically significant correlation was found in different age groups with adiponectin (p<0.001), glucose (p<0.001), and HbA1c (p<0.001).

The study analyzed linear regressions for each marker of carbohydrate metabolism. It was shown that the concentration of adiponectin significantly (p<0.001) increases with age (the results are pre-sented in Fig. 1). The results of the 1st and 3rd quartiles also tend to increase with age, with the dif-ference between them also increasing, doubling in the 89–99 group compared to the 18–29 group. Also, the assessment of Q1 and Q3 quartiles showed a considerable data variation (see Table 2).

Glucose levels also change significantly with age (p<0.001); Fig. 2. Q1 and Q3 also increase line-arly with age, while their differences also increase (see Table 2).

The analysis for HbA1c data showed a significant increase with age (p<0.001) in groups of healthy volunteers of the Russian population (Fig. 3). The Q1 and Q3 values also increased with age, and the gap between them remains roughly the same (see Table 2).

The concentrations of leptin (p=0.116), insulin (p=0.078), and CML (p=0.506) do not change sig-nificantly with age (Fig. 4–6). The data for Q1 and Q3 for leptin, insulin, and especially CML indi-cate a substantial data variation (see Table 2).

Discussion

This study aims to investigate the trends of carbohydrate metabolism biomarkers in different age groups of healthy individuals. Previous studies did not analyze a similar combination of indicators, especially in the Russian population. The combination of biomarkers in our study allows for a com-prehensive assessment of age-related changes in carbohydrate metabolism and adipose tissue. It was found that glucose, HbA_{1c}, and adiponectin levels significantly increase with age, while insulin, CML, and leptin concentrations do not change significantly.

Similar studies of adiponectin levels were conducted in Japan on a sample of 21,100 subjects and in the United States with the participation of 182 volunteers aged from 32 to 75 years [5, 7]. Despite the vast difference in the number of participants and the narrower age range in the second study, both studies showed a significant positive correlation between adiponectin level and age. The pro-posed underlying mechanism is a decrease in the rate of adiponectin biodegradation with age due to the deterioration of kidney function. The reported inverse relationship of the glomerular filtration rate with the adiponectin concentration supports this mechanism [8]. In a Polish study of 125 volunteers divided into groups by age and sex, considering the body mass index, there was no significant correlation between adiponectin level and age in females (p=0.5) and males; an increase in concentration was observed only at the age of over 70 years [8]. Compared with the RUSS-AGE study, the sample was much smaller, and the age distribution was

Table 1. General characteristics of the study group

Variable	Parameter	18–29 years (n=106)	30–39 years (n=107)	40–49 years (n=99)	50–59 years (n=106)	60–69 years (n=98)	70–79 years (n=92)	80–89 years (n=70)	90–97 years (n=33)	*P*-value (between groups, adjusted, FDR)
Age, years	Median (Q1–Q3)	25 (22–28)	34 (32–37)	44 (41-46.5)	54 (52-56.75)	64 (62–67)	74.5 (72–77)	84 (82–85)	93 (91–94)	<0.001
Sex (n=711), n (%)	Females	66 (62.26)	74 (69.16)	77 (77.78)	77 (72.64)	84 (84.85)	84 (91.3)	55 (78.57)	25 (78.12)	<0.001
	Males	40 (37.74)	33 (30.84)	22 (22.22)	29 (27.36)	15 (15.15)	8 (8.7)	15 (21.43)	7 (21.88)	
Type of residential place (n=711), n (%)	City	106 (100)	106 (99.07)	97 (97.98)	102 (96.23)	99 (100)	92 (100)	67 (95.71)	32 (100)	0.047
	Rural	0 (0)	1 (0.93)	2 (2.02)	4 (3.77)	0 (0)	0 (0)	3 (4.29)	0 (0)	
Co-residence (n=710), n (%)	Family	65 (61.32)	90 (84.11)	87 (87.88)	88 (83.02)	69 (69.7)	35 (38.04)	29 (42.03)	13 (40.62)	<0.001
	Boarding school/ nursing home/ residential care home, etc.	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1.45)	0 (0)	
	Single	23 (21.7)	13 (12.15)	12 (12.12)	17 (16.04)	29 (29.29)	57 (61.96)	39 (56.52)	18 (56.25)	
	Cohabitation (dormitory/with friends)	18 (16.98)	4 (3.74)	0 (0)	1 (0.94)	1 (1.01)	0 (0)	0 (0)	1 (3.12)	
Marital status (n=710), n (%)	Common-law marriage	10 (9.43)	11 (10.28)	9 (9.09)	7 (6.6)	4 (4.04)	1 (1.09)	1 (1.45)	0 (0)	<0.001
	Widowed	1 (0.94)	0 (0)	2 (2.02)	5 (4.72)	26 (26.26)	48 (52.17)	43 (62.32)	27 (84.38)	
	Married	24 (22.64)	63 (58.88)	62 (62.63)	64 (60.38)	40 (40.4)	14 (15.22)	14 (20.29)	3 (9.38)	
	Never been married	69 (65.09)	23 (21.5)	8 (8.08)	5 (4.72)	3 (3.03)	3 (3.26)	3 (4.35)	1 (3.12)	
	Di-vorced/ separated	2 (1.89)	10 (9.35)	18 (18.18)	25 (23.58)	26 (26.26)	26 (28.26)	8 (11.59)	1 (3.12)	
Education (n=710), n (%)	Higher	89 (83.96)	92 (85.98)	84 (84.85)	84 (79.25)	76 (76.77)	54 (58.7)	47 (68.12)	20 (62.5)	<0.001
	Basic or lower	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1.09)	1 (1.45)	4 (12.5)	
	Secondary	16 (15.09)	6 (5.61)	5 (5.05)	14 (13.21)	18 (18.18)	30 (32.61)	19 (27.54)	4 (12.5)	
	Academic degree	1 (0.94)	9 (8.41)	10 (10.1)	8 (7.55)	5 (5.05)	7 (7.61)	2 (2.9)	4 (12.5)	
Currently employed (n=710), n (%)	Yes	94 (88.68)	102 (95.33)	98 (98.99)	83 (78.3)	34 (34.34)	8 (8.7)	2 (2.9)	1 (3.12)	<0.001
	No	12 (11.32)	5 (4.67)	1 (1.01)	23 (21.7)	65 (65.66)	84 (91.3)	67 (97.1)	31 (96.88)	

not uniform, which could explain the difference in the results. Also, an increase in adiponectin in elderly men may be due to a gradual decrease in testosterone and dehydroepiandrosterone sulfate concentrations, which inhibit adipokine secretion [3, 5]. Given the growing prevalence of metabolic diseases with age, an increase in adi-ponectin may be protective [1]. Due to its anti-atherosclerotic, anti-inflammatory, and cardioprotective effects, as well as its ability to increase insulin sensitivity, adiponectin provides a more favora-ble aging profile [9].

In addition, centenarians, who are significantly less susceptible to metabolic disorders, have higher adiponectin concentrations [4].

Our study showed no significant change in leptin levels with age. However, a similar study demon-strated that the plasma level in patients older than 60 was reduced by 53% compared with the younger group [10]. The other two papers revealed sex differences in the trends of leptin. An Ameri-can study showed an age-related increase in leptin in females, without its change in males; in a Polish study, however, it increased in males and did not correlate with age in females [11, 12]. Com-pared to RUSS-AGE, both studies were conducted on much smaller samples, 70 and 114 subjects.

Our study showed a statistically significant increase in glucose, which was also found in other similar studies. One study included 771 subjects with their fasting and post-glucose tolerance test glucose levels measured [13]. In this study, the sample size and age range were close to those used in RUSS-AGE, which probably leads to similar results. Another study included 67 elderly and 21 young participants, which is significantly less than in RUSS-AGE, and also found a positive cor-relation with age (p<0.001) [14]. Despite different sample sizes and study designs, many studies demonstrated increasing glucose levels with age in healthy subjects. Presumably, this is due to a de-crease in its utilization rate, which, on the one hand, may be associated with an age-related decrease in metabolic activity [15]. On the other hand, it may be related to a decrease in tissue insulin sensi-tivity, both due to aging itself and age-related changes in body composition. In particular, the in-crease in adipose tissue is a serious risk factor for insulin resistance [1]. Also, with age, the function of pancreatic β-cells deteriorates, and the muscle tissue that consumes a significant part of glucose reduces [16].

In addition, our results show an increase in HbA1c with age. Similar results were shown in an anal-ysis of multiple linear regression in a study of 4,748 Taiwanese subjects aged 30 to 70 years [17]. An American study including 5,743 participants also showed a positive correlation with age, with an increase in HbA_{1c} of 0.010-0.014 units per year, depending on the population [18]. Also, the Chi-nese study using a linear regression analysis showed that HbA_{1c} levels increased by an average of 0.020% over 10 years. These data were obtained from 18,265 patients not previously diagnosed with DM [18].

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Table 2. Carbohydrate metabolism parameters in different age groups of the RUSS–AGE study

Marker, Me (Q1–Q3)	18–29 years (n=106)	30–39 years (n=107)	40–49 years (n=99)	50–59 years (n=106)	60–69 years (n=98)	70–79 years (n=92)	80–89 years (n=70)	90–97 years (n=33)	P–value (between groups, adjusted, FDR)
Adiponectin, µg/mL	13.42 (9.17–23.33)	13.52 (8.09–21.26)	11.48 (6.7–25.27)	12.32 (7.2–17.83)	11.94 (9.58–19.58)	23.16 (12.4–31.49)	23.8 (12.33–35.03)	31.49 (21.55–48.33)	<0.001
Leptin, ng/mL	14.58 (7.46–61.04)	15.23 (6.33–37.11)	19.54 (6.76–39.23)	13.84 (5.39–30.76)	13.41 (6.38–28.26)	18.41 (10.7–36.47)	25.18 (10.89–51.09)	27.07 (11.23–92.8)	0.116
HBA_{1c}, %	5.1 (4.9–5.3)	5.1 (4.9–5.4)	5.3 (5–5.6)	5.5 (5.3–5.7)	5.5 (5.4–5.8)	5.7 (5.43–5.9)	5.8 (5.57–6.2)	5.9 (5.55–6.1)	<0.001
Glucose, mmol/L	4.3 (4.06–4.56)	4.32 (4.16–4.59)	4.46 (4.26–4.89)	4.55 (4.26–4.92)	4.61 (4.34–5.02)	4.88 (4.57–5.28)	4.89 (4.56–5.6)	4.75 (4.5–5.41)	<0.001
Insulin, µU/mL	9.04 (6.78–12.34)	7.69 (6.12–10.37)	8.26 (5.68–11.09)	7.08 (5.31–10.45)	8.48 (6.32–11.84)	9.59 (6.67–12.25)	8.71 (6.31–12.16)	8.86 (6.04–12.95)	0.078
CML, ng/mL	216.35 (96.01–443.51)	155.84 (94.18–499.03)	181.02 (80.0–377.81)	227.06 (93.84–445.98)	199.16 (86.06–421.25)	236.62 (124.18–387.21)	281.74 (77.75–498.24)	180.36 (46.22–588.26)	0.506

Fig. 1. Changes in adiponectin levels with age.

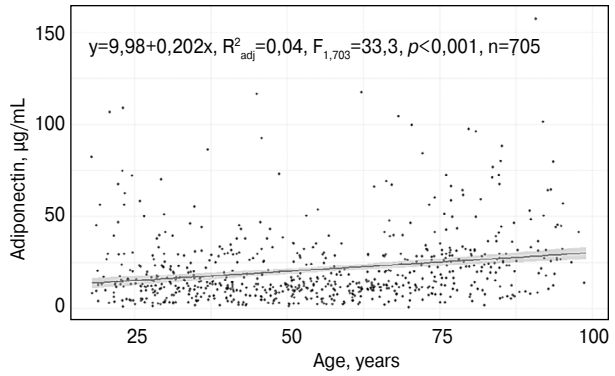


Fig. 2. Changes in glucose levels with age.

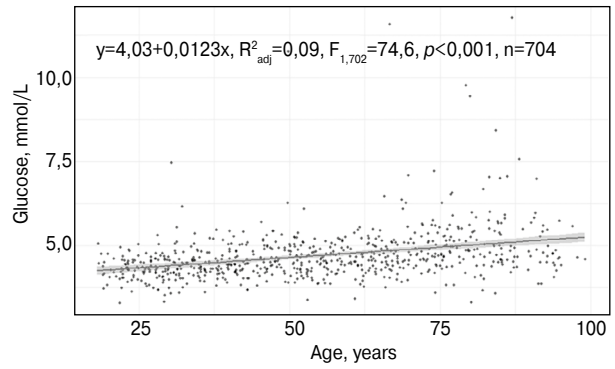


Fig. 3. Changes in HbA_{1c} with age.

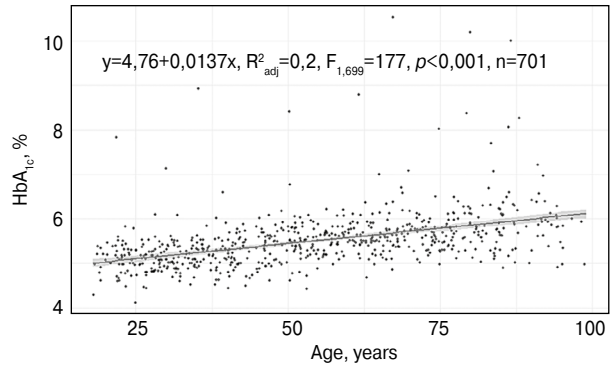
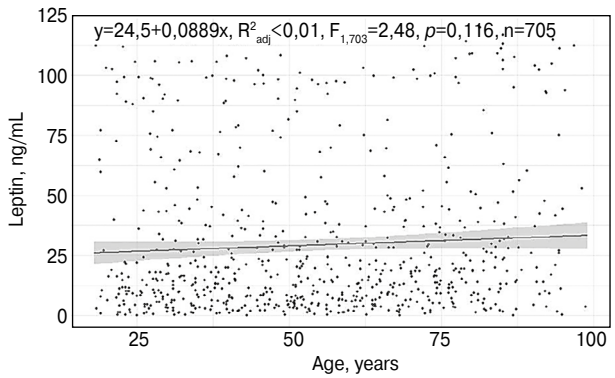


Fig. 4. Changes in leptin levels with age.



Thus, our findings align with the results of all these studies, including subjects of different nationalities, indicating that the found trend is consistent. These findings are likely due to age-related hyperglycemia, which leads to elevated HbA_{1c} levels [1]. A higher glycation rate associated with aging can also increase HbA1c [18].

The results showed no significant changes in insulin levels with age (p=0.078). In a study by D. Muller et al., which included 771 volunteers from 20 to 96 years of age, also no correlation was found between age and fasting insulin level [13]. Similar results were probably obtained due to the analysis of subjects of similar age ranges with a uniform distribution across age groups. In addition, two studies included isolated groups of young (23.7±0.8 years, 28±1 years) and elderly (70.1±0.7 years, 70±1 years) subjects with a total of 291 participants [14, 19]. The results of both studies showed that neither the fasting insulin concentration nor the peak concentration differed be-tween the groups. Therefore, despite the different study designs and sample sizes, the general trend towards a lack of correlation of insulin with age is consistent in many studies and is confirmed in our study. It has been shown that maintaining a stable low level of insulin and minimizing the activity of its signaling pathways contribute to an increase in life expectancy [2]. Centenarians have low fasting insulin levels and a higher insulin sensitivity compared to the elderly [4]. High insulin concentra-tions lead to cellular stress and premature aging due to excessive lipogenesis, accumulation of non-functional polypeptides, impaired autophagy, mitochondrial dysfunction, and elevated free radical levels [2].

According to our data, CML did not change significantly across the age groups (p=0.506); howev-er, other studies with similar designs showed that CML increased with age. One of the studies was conducted in China using 1,196 blood plasma samples from donors. It showed a significant positive correlation of CML level with age in males (p<0.001) but not in females (p=0.053) [20]. In contrast to our study, no sampling was exclusively from healthy patients, which could have biased

Fig. 5. Changes in insulin levels with age.

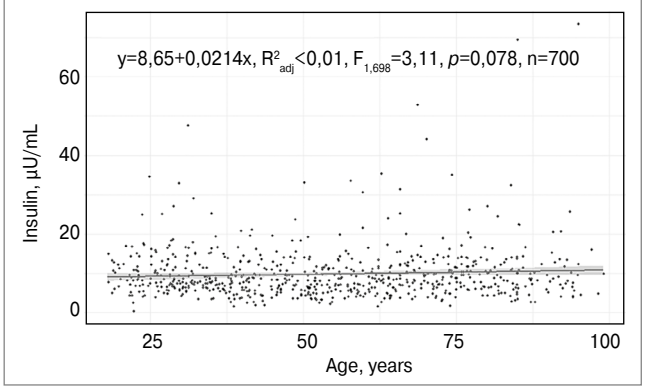
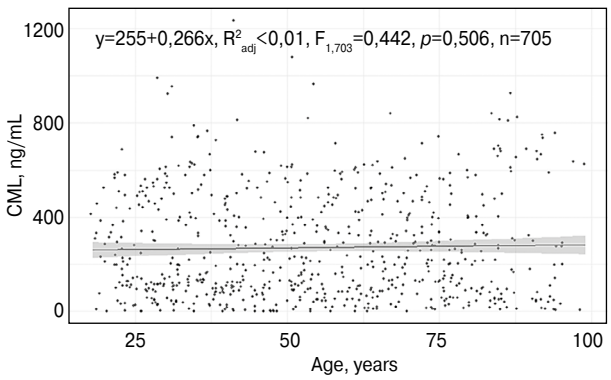


Fig. 6. Change in CML levels with age.



the results. The other two studies were conducted in the USA and included participants aged 18 to 45 and over 60 years; the number of participants was 325 and 172, respectively [21, 22]. Both studies, unlike RUSS-AGE, had small samples and also studied selected age groups, which is important to consider due to the large variability in CML levels according to our data. Also, both studies were conducted in the USA, where the typical diet differs significantly from the Russian diet, and the CML level is affected by its content in the food consumed [23]. CML accumulation adversely affects the body's condition due to its ability to damage tissues by modifying the protein structure and conformation, forming free radicals, and inducing chronic inflammation [3].

Conclusion

The study identified trends typical for healthy subjects aged 18 to 97 years. The absence of chang-es in leptin levels correlates with the data on the healthy aging of centenarians and may be due to maintaining a normal body mass index and adipokine sensitivity. The ability of adiponectin to coun-teract the development of diseases of the cardiovascular system and inflammation and its increase with age, presumably, can slow down the aging process, and its ability to improve insulin sensitivity could contribute to the absence of changes in the latter. With age, glucose and HbA_{1c} levels also increase in healthy individuals. Still, their median values should remain within the reference ranges to prevent hyper- or hypoinsulinemia and the accumulation of glycation end-products. However, prospective studies are necessary for definitive conclusions on the trends of carbohydrate metabo-lism markers in a healthy population of the Russian Federation.

Study limitations

One of the limitations was the sample composition since the study included mainly residents of Central Russia. The Russian Federation is a state with a large number and uneven distribution of people of different nationalities, which can also affect the nature of changes in carbohydrate me-tabolism with age.

Therefore, collecting data throughout the country considering this factor is necessary to create a rep-resentative sample of the Russian population.

Another limitation of the study was the number of participants in the age group of 89–99 years, which is significantly lower than the other groups. This is due to a low number of healthy individuals of old age. Therefore, it raises the question of the representativeness of the selected volunteers of old age. Starting from a certain age, study participants probably have more favorable health characteris-tics than the average person of the same age.

Disclosure of interest. The authors declare that they have no competing interests.

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Authors' contribution. The authors declare the compliance of their authorship according to the international ICMJE criteria. All authors made a substantial contribution to the conception of the work, acquisition, analysis, interpretation of data for the work, drafting and revising the work, final approval of the version to be published and agree to be accountable for all aspects of the work.

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Consent for publication. Written consent was obtained from the patients for publication of relevant medical information and all of accompanying images within the manuscript.

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