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THE EFFECT OF TOBACCO SMOKING ON HOMOCYSTEINE METABOLISM IN HEALTHY NICOTINE-DEPENDENT PEOPLE LIVING IN THE ARKHANGELSK REGION

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Abstract. ***Introduction.*** Tobacco smoking remains a global medical, social and economic problem worldwide. One of the pathological effects of nicotine and tobacco smoke components is the suppression of folate metabolism and a decrease in B vitamins in the human body, which, together, entails a violation of homocysteine metabolism and leads to endothelial dysfunction and the development of adverse vascular events. ***The purpose of the study*** — to identify the effect of tobacco smoking and the concentration of vitamins (B_6, B_9, B_{12}) on homocysteine metabolism in healthy young volunteers. ***Materials and methods.*** The study was carried out on a sample of ethnic Russians living in the city of Arkhangelsk. 259 healthy volunteers of both sexes of young age from 18 to 32 years old were included, a survey of participants was conducted, the levels of folic acid, vitamin B_6 and B_{12}, homocysteine were analyzed by immunological method. Statistical processing of the data obtained during the study was carried out by methods of descriptive and analytical statistics using the R 4.2.3 programming language in the Rstudio 1.2.5019 program. ***Results.*** There were no statistically significant differences in all defined indicators between the group of smokers and non-smokers. But the average homocysteine level in the smoker group is higher (Iu=8.00) than in the non-smoker group (Iu=7.00). At the same time, the participants who smoked cigarettes had higher homocysteine levels (Iu=8.6) than those who smoked electronic cigarettes (Iu=7.2). The average serum folic acid concentration in smokers is lower (Iu=4.00) than in non-smokers (Iu=6.5). In the group of smokers, folate deficiency was registered in 13 participants. Folic acid deficiency was not detected in the non-smoking group. An inverse relationship of average strength between the level of homocysteine and the concentration of folic acid in the blood serum ($p < 0.01$) was revealed. ***Conclusion.*** In this study, the relationship between smoking and homocysteine levels was not revealed, however, the average homocysteine level in the smoker group is higher than in the non-smoker group. The lack of correlation may be due to the short smoking experience, the small number of cigarettes smoked per day, the low smoker index and the young age of the study participants. It was revealed that the average homocysteine level in smokers of traditional cigarettes was higher than in participants using electronic tobacco heating systems.

Keywords: tobacco smoking, homocysteine, folate metabolism, B vitamins, Arkhangelsk Region

ВЛИЯНИЕ ТАБАКОКУРЕНИЯ НА ОБМЕН ГОМОЦИСТЕИНА У ЗДОРОВЫХ НИКОТИНЗАВИСИМЫХ ЛИЦ, ПРОЖИВАЮЩИХ НА ТЕРРИТОРИИ АРХАНГЕЛЬСКОЙ ОБЛАСТИ

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Резюме. ***Введение.*** Табакокурение во всем мире остается глобальной медико-социальной и экономической проблемой. Никотин и компоненты табачного дыма влияют на фолатный обмен, снижают уровень витаминов группы В, что в совокупности влечет за собой нарушение обмена гомоцистеина, приводя к развитию эндотелиальной дисфункции и неблагоприятных сосудистых событий. ***Цель исследования*** — выявить влияние табакокурения и концентрации витаминов группы В (B_6, B_9, B_{12}) на обмен гомоцистеина у здоровых добровольцев молодого возраста. ***Материалы и методы.*** Исследование выполнено на выборке этнических русских, проживающих на территории Архангельской области. Включено 259 здоровых добровольцев обоих полов молодого возраста от 18 до 32 лет, проведено анкетирование, анализ уровня фолиевой кислоты, витаминов B_6 и B_{12}, гомоцистеина методом иммуноферментного анализа. Статистическая обработка данных, полученных в ходе исследования, проводилась методами описательной и аналитической статистики с использованием языка программирования R 4.2.3 в программе Rstudio 1.2.5019. ***Результаты.*** Статистически значимых различий по всем анализируемым показателям между группами курящих и некурящих участников не выявлено. Среднее значение уровня гомоцистеина в группе курильщиков было выше (Me=8,00), чем в группе некурящих (Me=7,00), при этом у участников, курящих сигареты, уровень гомоцистеина был выше (Me=8,6), чем у курящих электронные сигареты (Me=7,2). Среднее значение концентрации фолиевой кислоты в сыворотке у курящих было ниже (Me=4,00), чем у некурящих (Me=6,5). В группе курильщиков дефицит фолатов отмечен у 13 участников, в группе некурящих дефицита фолиевой кислоты не выявлено. Выявлена обратная связь средней силы между уровнем гомоцистеина и концентрацией фолиевой кислоты в сыворотке крови ($p < 0,01$). ***Заключение.*** В данном исследовании взаимосвязь между курением и уровнем гомоцистеина не выявлена, вместе с тем среднее значение уровня гомоцистеина в группе курильщиков было выше, чем в группе некурящих. Отсутствие взаимосвязи, возможно, связано с малым стажем курения, небольшим числом выкуренных сигарет в день, низким индексом курильщика и молодым возрастом участников исследования. Выявлено, что у курящих традиционные сигареты средний уровень гомоцистеина оказался выше, чем у участников, использующих электронные системы нагревания табака.

Ключевые слова: табакокурение, гомоцистеин, фолатный обмен, витамины группы В, Архангельская область

INTRODUCTION

According to the World Health Organization (WHO), tobacco smoking kills almost half of people who use it [16]. Globally, more than 8 million people a year die from tobacco exposure, including 1.3 million non-smokers from the effects of secondhand smoke [16]. The results of numerous studies around the world confirm that tobacco smoking is a significant risk factor for the development of various pathological processes and conditions, primarily diseases of the cardiovascular, respiratory, genitourinary systems, as well as cancer and complications of pregnancy [4, 15].

It is shown that in nicotine-dependent persons the risk of atherosclerosis and myocardial infarction increases from 1.5 to 6 times compared to non-smokers. The proven adverse effects of nicotine on the cardiovascular system include its effect on the chemoreceptors of the sinocarotid zone, leading to reflex excitation of respiration and increased blood pressure, increased production of catecholamines, contributing to myocardial damage, cytotoxic effect on endothelial cells, realized through fixation of tobacco smoke components on the cell surface and formation of antibodies to them [9, 10].

It is proved that nicotine reduces the level of vitamin B_6 in the blood, which acts as a cofactor in the reactions of homocysteine transsulfuration. Pyridoxine deficiency leads to impaired neutralization of homocysteine in the body and, as a consequence, to an increase in the level of homocysteine in blood plasma [9]. It is important that nicotine has the ability to slow down the folate cycle, the main function of which is the remethylation of homocysteine into methionine, resulting in the accumulation of excess homocysteine in plasma [7].

Homocysteine, being an extremely cytotoxic substance, has various mechanisms of damaging effect on the cardiovascular system, leading to the development of

endothelial dysfunction. Thus, homocysteine damages endothelial cells, which leads to its destabilization and loosening of vessel walls, participates in the formation of atherosclerotic plaque, being a component of "foam cells", has mitogenic properties that contribute to the development of vascular wall stiffness. Excess homocysteine stimulates increased platelet aggregation, triggers the processes of hypercoagulation, is involved in the development of oxidative stress through the formation of active oxygen radicals that trigger the process of lipid peroxidation. Hyperhomocysteinemia leads to the accumulation of asymmetric dimethylarginine (ADMA), which is an inhibitor of endothelial NO synthetase, resulting in blocked production of nitric oxide (NO), a strong antiaggregant and vasodilator [1].

Numerous studies demonstrate the relationship between tobacco smoking and elevated homocysteine levels in the blood of patients with various cardiovascular diseases [5, 7]. From the position of preventive medicine, it is of particular interest to study the effect of tobacco smoking on homocysteine levels in healthy young people even before the realization of adverse vascular events.

AIM

To determine the effect of tobacco smoking and concentration of B vitamins (B_6, B_9, B_{12}) on homocysteine metabolism in healthy young volunteers.

MATERIALS AND METHODS

The prospective one-stage cross-sectional study was performed on a sample of ethnic russians living in the territory of the Arkhangelsk. The bases of the study were the Department of Clinical Pharmacology and Pharmacotherapy of the Federal State Budgetary Educational Institution of Higher Professional Education "Northern State Medical University", the Regional Center of Antithrombotic Therapy of the State Budgetary Institution of Health Care "The First City Clinical Hospital named after E.E. Volosevich".

Inclusion criteria: healthy volunteers of Russian nationality of both sexes of young age (18 to 32 years); the absence of chronic diseases associated with endothelial dysfunction; the absence of pregnancy; the absence of taking medications, dietary supplements, vitamin complexes; written voluntary informed consent for participation in the study. *Exclusion criteria:* refusal to participate at any stage of the study.

The complex clinical and laboratory study included 259 volunteers, the participants were questioned. The level of folic acid, vitamins B_6 and B_{12}, homocysteine was analyzed by immunoenzymatic analysis. The study was approved by the local ethical committee of the Northern State Medical University (protocol No. 01/02-23 of 15.02.2023).

The level of homocysteine in serum was determined by solid-phase enzyme-linked immunosorbent assay using ELISA Kit For Homocysteine (HCy) reagents (Claud-Clone Corp., USA). Folate AccuBind ELISA reagents (Monobind, USA) were used to determine folic acid concentration. The reference interval, located in the range from 3.2 to 13.7 ng/mL, was considered as sufficient level of folic acid in serum. Concentration less than 3.2 ng/mL was defined as low level of folic acid. In order to determine the level of pyridoxine and cobalamin in blood, ELISA Kit For Vitamin B (VB_6) and ELISA Kit For Cyanocobalamin (CNCbl) (Claud-Clone Corp., USA) were used. Laboratory studies were performed at the laboratory of the First City Clinical Hospital named after E.E. Volosevich.

Statistical processing of the data obtained during the study was performed by methods of descriptive and analytical statistics using the programming language R 4.2.3 in the program Rstudio 1.2.5019. The nature of data distribution was assessed using the Shapiro-Wilk criterion. The data distribution was considered to be different from the normal distribution (Gaussian distribution) when the statistical significance level (p) was less than 0.05. The arithmetic mean (M) and standard deviation (σ) in the format of M±σ were used to describe the obtained data whose distribution did not differ from the Gaussian distribution. Data whose distribution differed from the Gaussian distribution are presented as median (Me), the first (Q1) and the third (Q3) quartiles. The Mann–Whitney criterion was used to compare independent samples with a distribution type that differed from the normal distribution. Differences between groups were considered statistically significant when the p-value (p) was less than 0.05. The Spearmans rank correlation coefficient was used to assess the relationship between two variables.

RESULTS

The study included 259 participants. The gender distribution of the participants was as follows: the proportion of women was 68.0% (n=176), men proportion was 32.0% (n=83). The age of the participants ranged from 21 to 30 years (Me=23 [22;28]). During the study, the sample was divided into two groups. The first group included non-tobacco smoking participants (n=137) and the second group included tobacco smoking participants (n=122). Serum levels of homocysteine, folic acid, vitamins B_6 and B_{12} were assessed in all participants. The results of the study and characterization of the study groups are presented in Table 1.

Table 1

Results of the study and characteristics of the groups (n=259)

Таблица 1

Результаты исследования и характеристика групп (n=259)

Показатель / Indicator	Некурящие участники (n=137) / Non-smoking participants (n=137)	Курящие участники (n=122) / Smoking participants (n=122)	p-значение / p-value
Возраст, годы / Age, years	Me=22 [22;28]	Me=23 [22; 26]	0,68
Индекс массы тела / Body mass index	Me=22,9 [20,0; 25,8]	Me=23,5 [20,6; 26,2]	0,72
Уровень фолиевой кислоты в сыворотке (нг/мл) / Serum folic acid level (ng/ml)	Me=6,5 [4,5; 8,0]	Me=4,00 [3,05; 6,00]	0,48
Уровень гомоцистеина в сыворотке крови (мкмоль/л) / Serum homocysteine level (mmol/l)	Me=7,0 [5,7; 10,0]	Me=8,00 [6,5; 9,0]	0,13
Уровень витамина B_6 в сыворотке крови (нг/мл) / Serum vitamin B_6 level (ng/ml)	Me=18,7 [15,8; 21,0]	Me= 8,2 [13,8; 22,3]	0,92
Уровень витамина B_{12} в сыворотке крови (пг/л) / Serum vitamin B_{12} level (pg/l)	Me=558 [384; 635]	Me=529 [329; 752]	0,74

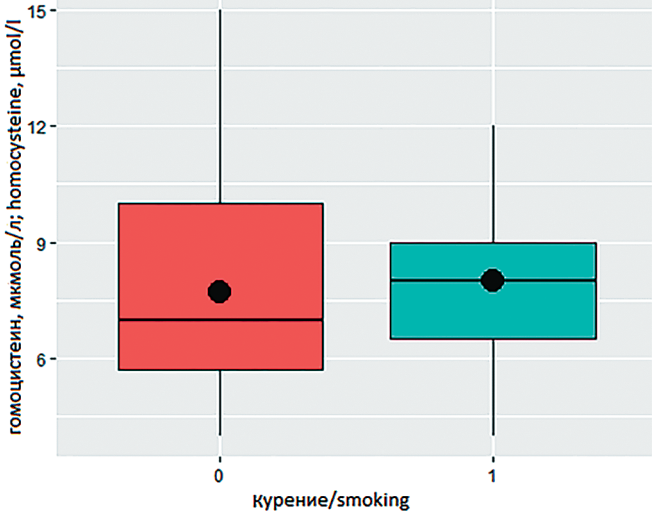

Fig. 1. The relationship between serum homocysteine levels and smoking

Рис. 1. Взаимосвязь уровня гомоцистеина в сыворотке крови и курения

Nicotine delivery to the body in the group of smokers in 68% of cases was due to electronic systems of heating tobacco, in 32% by the traditional way, with the cigarettes. Smoking experience in the smoking group averaged 3.5 years but did not exceed 5 years, and the number of cigarettes smoked per day ranged from 3 to 10. The smoking index of the cigarette-smoking participants ranged from 0.75 to 2.5 packs/year.

Comparative analysis of the groups showed that the body mass index (BMI) of the participants in the first and second groups did not differ. 85% of the participants of the first and the second groups had normal BMI (18.5–25.0), 15% of the participants of both groups were overweight (26.0–29.5), and BMI over 30, indicating the obesity, did not occur in the study sample.

The level of folic acid, homocysteine, vitamins B_6 and B_{12} in blood serum was determined in all study participants. No statistically significant differences in all determined parameters between the analyzed groups were found. It is important to note that the mean value of homocysteine level in the group of smokers was higher (Me=8.00) than in the group of non-smokers (Me=7.00). Participants smoking cigarettes having higher homocysteine levels (Me=8.6) than those smoking electronic cigarettes (Me=7.2). All participants in the first and the second groups had homocysteine levels within the reference values of 5.0 to 10.0 µmol/L. The data is presented in Figure 1.

A similar trend was observed in folate levels. Thus, the mean value of serum folate concentration in smokers was lower (Me=4.00) than in nonsmokers (Me=6.5). In addition, folate deficiency, where serum folic acid concentration was less than 3.2 ng/mL, was recorded in 13 participants in the smokers group. No folic acid deficiency was found in the non-smoker group.

The relationship between homocysteine levels and smoking and between homocysteine levels and folic acid concentration was analyzed. The data is presented in Figure 2.

The study revealed an inverse relationship of medium strength between homocysteine level and serum folic acid concentration ($p < 0.01$): the lower the folic acid level

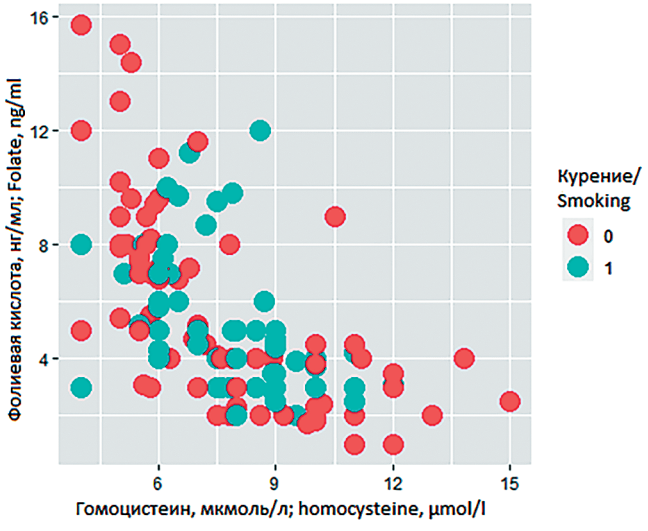

Fig. 2. **The relationship between homocysteine levels, smoking and serum folate concentrations**

Рис. 2. **Взаимосвязь уровня гомоцистеина, курения и концентрации фолиевой кислоты в сыворотке крови**

was, the higher the serum homocysteine level was. No relationship was found between serum homocysteine levels and smoking in this study (p=0.13).

DISCUSSION

Research data from recent years show that among young people under 30 years of age who smoke, the leading method of nicotine-containing product delivery is via various electronic systems such as vape, vaporizer, electronic cigarette and others [6, 8]. Our study also confirms this trend. Among the smoking participants, 68% used electronic nicotine delivery systems to deliver nicotine to the body. It is known that electronic nicotine delivery systems do not contain many toxic components of tobacco smoke, which are usually formed in cigarette smoke during combustion, but at the same time have in their composition such carcinogenic substances as formaldehyde, acetaldehyde, acetone, nitrosamines, propylene glycol, glycerol, phenols, and others. The nicotine in tobacco is addictive and dependent, which is especially dangerous for young people. Electronic devices, like normal cigarettes, contain high concentrations of nicotine, which has an extremely negative impact on the health of smokers [3, 11, 13].

At present, there is accumulated evidence of the effect of tobacco smoking on the level of homocysteine in the blood. It has been shown that homocysteine levels are significantly higher in healthy smokers than in nonsmokers [5, 14]. Evidence is presented that homocysteine levels depend on the number of cigarettes smoked per day, smoking history, and smoker's index. Each cigarette smoked increases homocysteine levels by 0.5% in men and 1% in women [2, 9]. In our study, there was a tendency to increase homocysteine levels in the smoking group, where the mean value of homocysteine levels in the smoking group was higher (Me=8.00) than in the non-smoking group (Me=7.00), however, no statistically significant difference could be obtained. No hyperhomocysteinemia condition was registered in any participant of the group. The absence of statistically significant differences in homocysteine levels in the first and second groups may be due to the short smoking experience (up to 5 years), as well as low smoking index (from 0.75 to 2.5 packs/year) in the participants of the second group, as well as the young age of the study subjects. No relationship between smoking and homocysteine levels was found in this study, but an average value of homocysteine levels in the group of smokers was higher than in the group of nonsmokers.

Folic acid is the most important determinant of the folate cycle, which results in the remethylation of homocysteine into methionine. There are many domestic and foreign studies on the role of folic acid in homocysteine metabolism. Folate deficiency leads to accumulation of the sulfur-containing amino acid homocysteine in the body, which in turn leads to endothelial dysfunction and development of adverse vascular events [12]. In our study, a statistically significant inverse relationship of medium strength between homocysteine level and serum folic acid concentration was confirmed.

CONCLUSION

1. The study revealed the effect of serum folic acid concentration on homocysteine level, while the effect of vitamin B_6 and B_{12} concentration was not found.

2. The mean value of homocysteine level in the group of smokers was higher than in the group of non-smokers, but tobacco smoking had no statistically significant effect on the serum homocysteine level.

ADDITIONAL INFORMATION

Author contribution. All authors confirm the conformity of their authorship, according to the international criteria of the ICMJE (all authors made a significant contribution to the development of the concept, conduct of the study and preparation of the article, read and approved the final version before publication). The largest contribution is distributed as follows: concept and design of the study — N.A. Vorobyeva, A.S. Vorontsova; collection and mathematical analysis of data — A.S. Vorontsova, E.Yu. Melnichuk; literature review,

manuscript preparation — A.S. Vorontsova, N.A. Vorobyeva, A.I. Vorobyeva.

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Consent for publication. Written consent was obtained from the patient for publication of relevant medical information within the manuscript.

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Вклад авторов. Все авторы подтверждают соответствие своего авторства, согласно международным критериям ICMJE (все авторы внесли существенный вклад в разработку концепции, проведение исследования и подготовку статьи, прочли и одобрили финальную версию перед публикацией). Наибольший вклад распределен следующим образом: концепция и план исследования — Н.А. Воробьева, А.С. Воронцова; сбор и математический анализ данных — А.С. Воронцова, Е.Ю. Мельничук; литературный обзор, подготовка рукописи — А.С. Воронцова, Н.А. Воробьева, А.И. Воробьева.

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