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IMPACT OF SYSTEMIC USE OF ELECTRONIC CIGARETTES ON THE LEVELS OF TOXIC AND POTENTIALLY TOXIC METALS IN SALIVA AMONG YOUNG PEOPLE

Abstract. The medical aspects of using electronic cigarettes (e-cigarettes) remain a topic of heated debate among the scientific community. Currently, there are gaps in their safety, which has led interested parties to conduct aggressive marketing campaigns to popularize them among the youth. The potential danger may stem from substances emitted during the use of e-cigarettes, which can harm both the user and those in their vicinity. Objective: To investigate the impact of regular use of electronic heated tobacco products on the levels of toxic and conditionally toxic metals in the saliva of young individuals who use e-cigarettes. Materials and Methods: The study involved 102 participants (main group - 66 individuals who used electronic heated tobacco products (EHTPs) as an alternative to smoking; control group - 36 individuals who had never smoked) aged 20-35 years. The study was conducted in accordance with the principles of bioethics outlined in the Helsinki Declaration on "Ethical Principles for Medical Research Involving Human Subjects" and the UNESCO Universal Declaration on Bioethics and Human Rights. Results and Discussion: In our study, it was found that the average levels of potentially toxic metals, such as silver and indium, in the saliva of EHTP users were likely higher, specifically 26.6% higher for silver ($p=0.039$) and 80.9% higher for indium ($p=0.005$), compared to non-smokers. For the toxic metal cadmium, the average level of its content in the saliva of EHTP users was 24.2% higher than in non-smokers ($p=0.001$). The study of local immunity in young individuals in the main and control groups showed that a decrease in the level of secretory IgA in the oral cavity secretion was detected in 56.7% of patients in the main group. Conclusions: In the saliva of young individuals using electronic cigarettes, there is an increase in silver content by 26% ($p=0.039$), indium by 80.9% ($p=0.005$), and cadmium by

24.2% (p=0.001) compared to non-smokers. A decrease in secretory IgA in the oral cavity secretion is observed in 56.7% of electronic cigarette users compared to 30% of non-smokers (p=0.033). The decrease in secretory IgA content in the saliva of electronic cigarette users is influenced by toxic metals, namely IgAl (r=0.230 p=0.047), Ba (r=0.268 p=0.025), Pb (r=0.255 p= 0.031), Sr (r=0.268 p= 0.025).

Keywords: electronic cigarettes, saliva metals, local immunity, young people.

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ВПЛИВ СИСТЕМНОГО ВЖИВАННЯ ЕЛЕКТРОННИХ СИГАРЕТ НА ВМІСТ ТОКСИЧНИХ ТА УМОВНО ТОКСИЧНИХ МЕТАЛІВ СЛИНИ У МОЛОДИХ ОСІБ

Анотація. Медичні аспекти вживання електронних сигарет (e-cigarettes) досі залишаються темою гарячих дискусій серед наукового суспільства. Наразі існують пробіли щодо безпечності їх використання, завдяки чому зацікавлені особи проводять жорстку рекламну кампанію з їх популяризації серед молоді. Потенційну небезпеку можуть становити речовини, які виділяються під час використання e-cigarettes, від чого може страждати як користувач, так і його оточення. Мета: дослідити вплив систематичного вживання тютюнових виробів електричного нагрівання на вміст токсичних та умовно-токсичних металів у слині молодих осіб, які палять електронні сигарети. Матеріали та методи: у дослідженні прийняло участь 102 особи (основна група - 66 осіб, які у якості альтернативного виду тютюнопаління використовували тютюнові вироби електричного нагрівання (ТВЕН-и); група контролю - 36 осіб, які ніколи не курили) віком 20-35 років. Дійсне дослідження було проведено відповідно до принципів біоетики, викладених у Гельсінській декларації «Етичні принципи медичних досліджень за участю людей», «Загальній декларації про біоетику та права людини (ЮНЕСКО)». Результати та обговорення. В нашому дослідженні виявлено, що середній рівень таких потенційно токсичних металів, як срібло та індій, у слині курців ТВЕН-ів є вірогідно вищим, а саме на 26,6 % вище для срібла (p=0,039) та на 80,9% вище для індію (p=0,005), ніж у тих, хто не курить. Для токсичного металу кадмію, середній рівень його вмісту у слині курців на 24,2% вище ніж у тих, хто не

курить (p=0,001). Дослідження стану місцевого імунітету у молодих осіб основної та групи контролю показав, що зниження рівня секреторного IgA в секреті ротової порожнини виявлено у 56,7% пацієнтів з основної групи. Висновки. У слині молодих осіб, що використовують електронні сигарети має місце підвищення вмісту срібла на 26% (p= 0,039), індію на 80,9% (p=0,005), кадмію на 24,2% (p=0,001) у порівнянні з тими, хто не палить. Зниження секреторного Ig A в секреті ротової порожнини має місце у 56,7 % користувачів електронних сигарет проти 30 % тих, хто не курить (p=0,033). На зниження вмісту секреторного Ig A у слині курців електронних сигарет мають вплив токсичні метали, а саме Ig Al (r=0,230 p=0,047), Ba (r=0,268 p=0,025), Pb (r=0,255 p= 0,031), Sr (r=0,268 p= 0,025).

Ключові слова: електронні сигарети, метали слини, місцевий імунітет, молодь.

Introduction. The use of electronic cigarettes (e-cigarettes) has become a widespread phenomenon in the modern world and has garnered significant interest in the context of health and safety. At present, there is insufficient clinical evidence regarding the safety of e-cigarette use, and tobacco companies are conducting extensive marketing campaigns, particularly targeting young individuals, to promote smoking devices. New electronic tobacco products are marketed by manufacturers as safe modern gadgets, often depicted against the backdrop of a healthy lifestyle. Surveys of a substantial number of individuals regarding their attitudes towards electronic cigarettes indicate that adolescents and young people do not perceive such smoking as a health risk [1, 2].

One of the key issues associated with e-cigarette use is the likelihood of a high content of heavy metals in the aerosol inhaled by users and bystanders. It is known that metals such as nickel (Ni), cadmium (Cd), lead (Pb), chromium (Cr), and others may be included in the composition of heating elements, liquid reservoirs, and other components of electronic cigarettes [3, 4]. In turn, the balance of micro and macroelements is of paramount importance to support human health since an imbalance, including in saliva, is linked to the risk of developing respiratory tract diseases, oral cavity conditions, and disruptions in mental development [5, 6].

Objective: To investigate the impact of regular consumption of electrically heated tobacco products on the levels of toxic and potentially toxic metals in the saliva of young individuals who use electronic cigarettes.

Materials and Methods: In accordance with the objectives of the present study, a total of 102 individuals were examined (main group - 66 individuals who used electrically heated tobacco products (EHTPs) as an alternative form of smoking; control group - 36 individuals who had never smoked) aged between 20 and 35 years.

Inclusion Criteria for the Main Observation Group:

- General somatic health status.

- Individuals aged 20-35 years.
- Systematic use of EHTPs (electrically heated tobacco products).
- Absence of acute or chronic diseases, including exacerbations of chronic respiratory tract infections.

Exclusion Criteria from the Main Observation Group:

- Presence or exacerbation of chronic illnesses.
- Smoking of industrial ("traditional") cigarettes.
- Age below 18 or above 35 years.

The actual study was conducted in accordance with the principles of bioethics outlined in the Helsinki Declaration on "Ethical Principles for Medical Research Involving Human Subjects" and the UNESCO Universal Declaration on Bioethics and Human Rights.

A comparison of demographic characteristics between individuals in the main group (n=66; males - 60.6%, females - 39.4%) and the control group (n=36; males - 27.8%, females - 72.2%) is presented in Table 1.

Table 1

Characteristics of participants in the main and control groups by age and gender

Indicator	Main group (n=66)	Control group (n=36)	p-level
Age, entire group M (SD)	24.4 (3.5)	24.2 (3.1)	0.316626
Age, males M (SD)	24.8 (3.9)	26.3 (4.5)	0.17716
Age, females M (SD)	23.8 (2.8)	23.6 (2.4)	0.382251
Number of individuals, males, %	60.6	27.8	0.003054
Number of individuals, females, %	39.4	72.2	

Informed Consent: Informed consent for participation in the study was obtained from all participants.

Methodologies and Investigations: To accomplish the study objectives, the following methodologies were employed:

Measurement of metal levels in saliva: the evaluation of metal levels in saliva was conducted at the laboratory of the Scientific Research Center "Center," under the auspices of the State Institution "Dnipro Medical Academy of the Ministry of Health of Ukraine," utilizing the method of inductively coupled plasma atomic emission spectrometry (ICP-AES). Multi-element standards for ICP VIII Certipur® (diluted in nitric acid) were utilized as standard solutions. The following metal ion contents were determined in the oral cavity secretion:

- Toxic metals: Aluminum, lead, barium, thallium, cadmium, strontium, bismuth.
- Potentially toxic metals: Silver, gallium, indium.

Saliva Collection: saliva (oral cavity secretion) was collected between 8 and 11 AM. Donors were instructed to rinse their mouth with 100 mL of distilled water before sample collection. Subsequently, 5 mL of unstimulated saliva was collected in plastic tubes placed on ice and stored at a temperature of -20°C until the moment of analysis in the laboratory.

Measurement of secretory IgA and Lysozyme levels: the measurement of secretory IgA and lysozyme levels was conducted at "Medical Academy Pharmacies" LLC using a photometer for microplates HiPo MPP-96. This was done with the assistance of DKO078IgA Saliva ELISA DiaMetra Italy test systems and Human LZM (Lysozyme) ELISA Kit Elabscience.

Statistical Analysis: Statistical analysis of the obtained results was carried out using traditional methods of variation statistics with the use of licensed programs Microsoft Excel and SPSS v.23. Given that more than 90% of the data deviated significantly from a normal distribution, preference was given to non-parametric statistical methods. The obtained results were considered statistically significant at a level of statistical significance (p) less than 0.05.

Results and Discussion: In accordance with the objectives of the present study, we conducted a comparison of levels of toxic and potentially toxic metals in the saliva of individuals who use heated tobacco products (HTPs) and individuals who have never smoked (Table 2).

For all parameters, the content of toxic and potentially toxic metals, which differed, was higher in users of electronic cigarettes compared to individuals who have never smoked.

Table 2

Statistical difference in levels of toxic and potentially toxic metals in the saliva of young individuals in the main and control groups

Metal (μg/mL)	p-level
Potentially toxic metals	
Indium	0.005*
Silver	0.039*
Gallium	not detected
Toxic metals	
Cadmium	0.001*
Aluminum	0.362
Bismuth	0.060
Lead	0.269
Strontium	0.288
Thallium	not detected
Barium	0.652

* - statistically significant difference at the level of $p < 0.05$

Based on our data, the average levels of potentially toxic metals, such as silver and indium, in the saliva of HTP users were significantly higher, namely 26.6% higher for silver (p=0.039) and 80.9% higher for indium (p=0.005), compared to those who do not smoke (Figure 1). For the toxic metal cadmium, the average level in the saliva of HTP users was 24.2% higher than in non-smokers (p=0.001) (Figure 3). It should be noted that toxic metals such as aluminum, lead, barium, strontium, and bismuth were detected in the saliva of young individuals in both study groups, but we did not find a statistically significant difference in their content, while thallium and gallium were not detected in the saliva of both the main and control groups in our study (p>0.05).

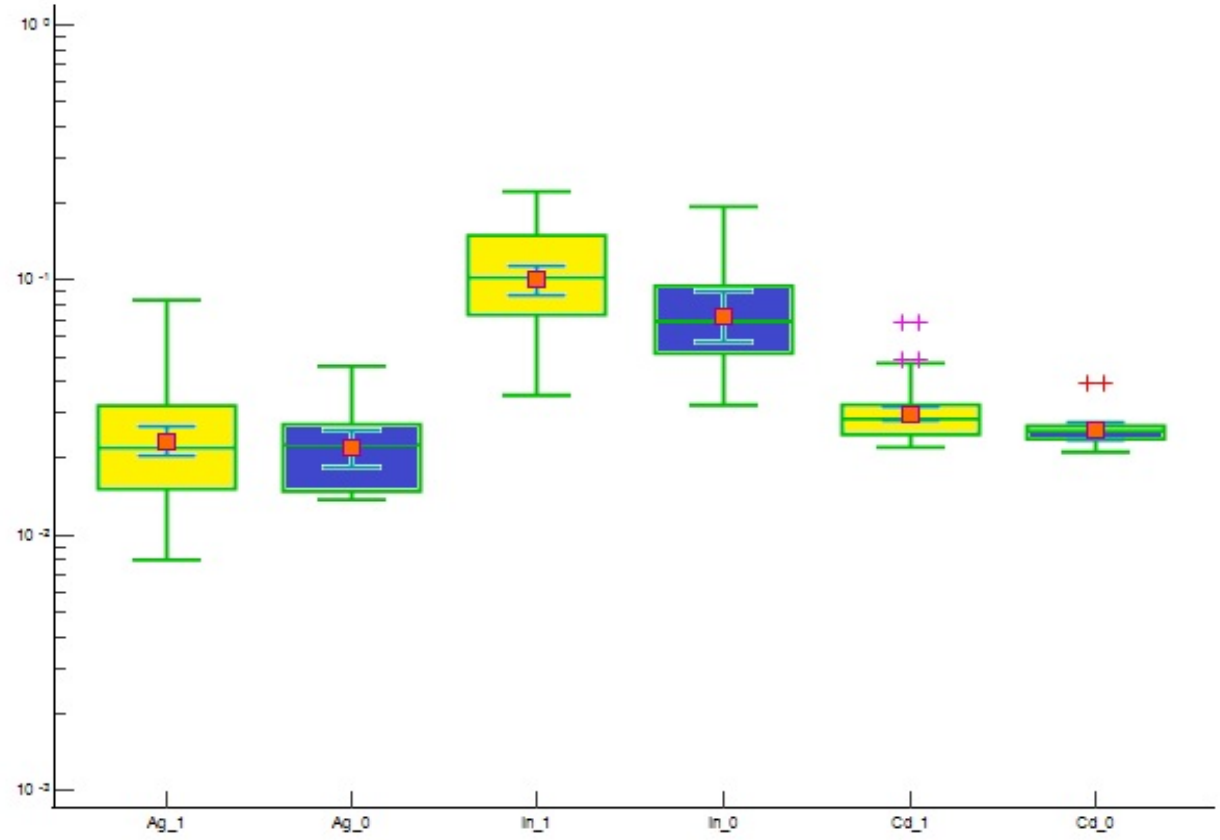

Fig.1. *Comparison of mean saliva metal levels in participants of the main (yellow) and control (blue) groups*

The study of the local immune system in young individuals from the main and control groups showed that a decrease in the level of secretory IgA in the saliva was detected in 56.7% of patients in the main group and in 30% of cases in the control group.

In accordance with the objectives of our study, we conducted a correlation analysis between the studied parameters, which allowed us to identify direct interactions between various toxic and potentially toxic metals in saliva and the concentration of secretory IgA (Figure 2), as one of the markers of the local immune system.

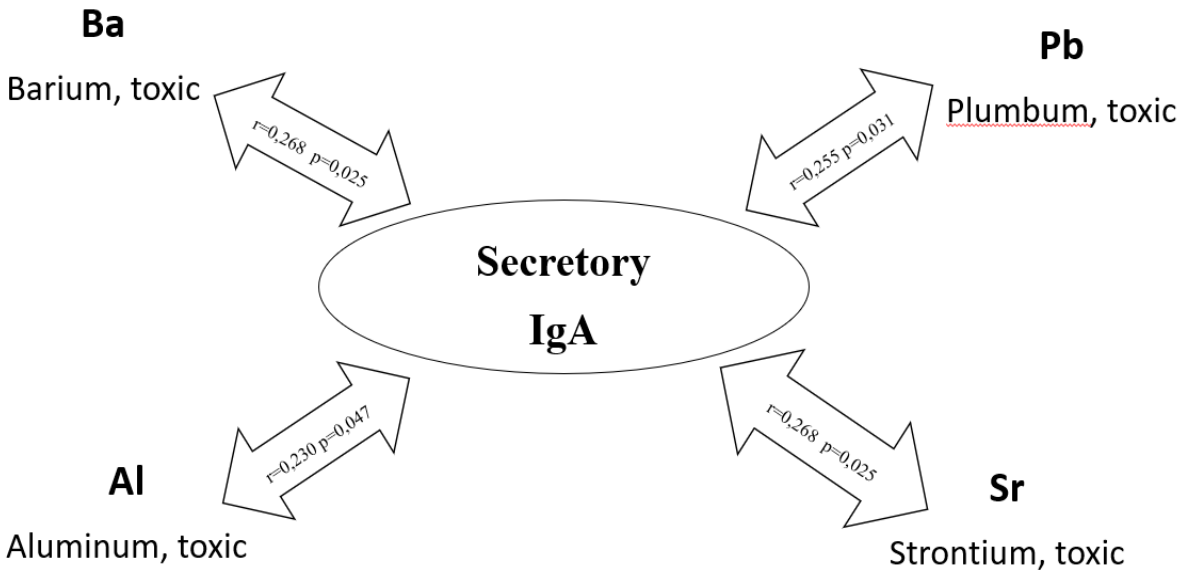

Fig. 2. *Correlation matrix of relationships between toxic metals and local immunity indicator*

According to our data and the results of the conducted correlation analysis, there is a connection between the phenomenon of systematic use of this type of tobacco smoking by EHTPs users and an increase in only toxic metals. This suggests a potential risk of these compounds impacting the health of young individuals who use electronic cigarettes.

Based on the literature, heavy metals such as nickel (Ni), cadmium (Cd), lead (Pb), chromium (Cr), and others can be incorporated into the composition of heating elements, liquid tanks, and other components of electronic cigarettes.

It is well-established that lead, mercury, aluminum, cadmium, and arsenic, as well as certain pesticides, are known to cause damage to the brain and are closely associated with neurodegenerative diseases such as Alzheimer's disease, amyotrophic lateral sclerosis (ALS), Huntington's disease, multiple sclerosis, and Parkinson's disease (Chen et al., 2016; Chen-Chan et al., 2015) [7].

Cadmium is a trace element that does not have a nutritional function for humans (Newman-Taylor 1998), and according to the Toxicological Profile for Cadmium from the Agency for Toxic Substances and Disease Registry (ATSDR 1999), it is a probable human lung carcinogen. The toxicity of cadmium to the lungs has been well-documented in animal studies. For example, inhalation of cadmium induces lung inflammation in mammals (Kirschvink et al. 2006), and daily doses of cadmium aerosol at 1.6 mg/m3 over a six-week period have been associated with acute lung damage. Therefore, animal studies on lung toxicity support the hypothesis that reduced lung function in smokers may be partially linked to the presence of cadmium in cigarette smoke. Primary non-occupational sources of cadmium exposure in the population include the consumption of contaminated food (Järup et

al., 1998; Kido et al., 1992) and the inhalation of cigarette smoke (Järup et al., 1998; Satarug and Moore, 2), resulting in higher cadmium levels in the body than in non-smokers (Erzen and Kragelj, 2006; Grasseschi et al., 2003; Järup et al., 1998; Mutti et al., 2006) [8].

Нещодавнє дослідження показало можливу участь кадмію у розвитку Recent research has indicated the potential involvement of cadmium in the development of lung diseases such as chronic obstructive pulmonary disease (COPD) and emphysema [8]. Animal studies have shown that cadmium chloride can reduce lung vital capacity and increase the thickness of alveolar walls. Inhalation of cadmium vapors in the absence of antioxidants and under conditions of oxidative stress can lead to lung inflammation and emphysema [8]. According to the Agency for Toxic Substances and Disease Registry (ATSDR), cadmium is considered a potential human lung carcinogen [9].

Indium (In) is primarily used in the form of indium tin oxide, which possesses unique transparency properties and is essential in the production of liquid crystal displays. The lung toxicity of indium compounds in humans was not recognized until the past two decades. In Japan, several cases of lung diseases associated with indium exposure were registered in individuals referred to as "indium lung." The main pathological manifestations included interstitial pneumonia, emphysema, and granulomas containing cholesterol crystals. In 2010, three cases of alveolar proteinosis were reported in the United States and China. As of March 2019, over 10 cases of interstitial pneumonia in the lungs have been documented.

Cross-sectional studies of workers handling indium have shown that the concentration of indium in serum (sIn) is closely related to the duration of exposure, the extent of interstitial and emphysematous lung changes based on high-resolution computed tomography (HRCT), and serum biomarkers of interstitial pneumonia, including surfactant protein-D (SP-D) [10].

Conclusions:

1. Saliva analysis of young individuals who use electronic cigarettes reveals an increase in silver content by 26% (p=0.039), indium by 80.9% (p=0.005), and cadmium by 24.2% (p=0.001) compared to non-smokers.

2. A decrease in secretory IgA in the oral cavity's secretion is observed in 56.7% of electronic cigarette users compared to 30% of non-smokers (p=0.033).

3. The reduction in secretory IgA levels in the saliva of electronic cigarette users is influenced by toxic metals, specifically IgAl (r=0.230, p=0.047), Ba (r=0.268, p=0.025), Pb (r=0.255, p=0.031), and Sr (r=0.268, p=0.025).

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