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Article

The Role of Tobacco in The Development of Nicotine Palatine Leukoplakia

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Abstract: Nicotine, the principal alkaloid in tobacco leaves, constitutes approximately 95% of all alkaloids in cigarettes and is the primary agent responsible for tobacco addiction. Tobacco products vary in nicotine content, with pipe tobacco containing similar levels to cigarettes, while cigars and chewing tobacco contain less. Nicotine is rapidly absorbed depending on its pH and the route of exposure, accumulating in the brain, saliva, gastric juice, liver, lungs, kidneys, and crossing the placental and mammary barriers. The metabolic rate of nicotine, influenced by factors such as age, gender, nutrition, pregnancy, and CYP2A6 genetic polymorphism, determines the intensity of addiction and the success of cessation attempts. Chronic exposure to tobacco smoke introduces thousands of toxic compounds that affect cardiovascular, respiratory, and immune systems. Nicotine dependence manifests through withdrawal syndrome, increased tolerance, persistent desire for tobacco use, and continued consumption despite harmful effects. Early identification of nicotine addiction using standardized diagnostic criteria and assessment tools, such as the Fagerström Test, is crucial for effective interventions. This study examines the role of tobacco in the development of nicotine-induced palatine leukoplakia, emphasizing pathophysiological mechanisms, systemic distribution of nicotine, and clinical implications for prevention and treatment.

Keywords: Tobacco, Oral Cavity, Smoking, Gingivitis, Toothpastes

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1. Introduction

The low availability of medical care for tobacco smoking and the unwillingness of medical professionals to provide the necessary information on the treatment of nicotine addiction and the consequences of tobacco smoking is a consequence of the lack of uniform requirements for the organization of medical care and training of doctors of various specialties on this topic[1].

Nicotine is the main alkaloid of tobacco leaves, its content in cigarettes is approximately 95% of all alkaloids contained in this plant, of which there are more than a dozen. It is the main inducer of tobacco addiction. Tobacco products differ in nicotine content. Pipe tobacco contains about the same amount of nicotine as regular cigarettes, while cigars and chewing tobacco contain less nicotine. The harm caused to the body by tobacco smoking is mostly related to inhaled cigarette smoke, which contains various chemicals, toxic combustion products that negatively affect the cardiovascular, respiratory, and immune systems. Gorenje More than 4,000 chemicals have been identified in tobacco smoke, of which about 250 are dangerous to health and more than 50 can cause cancer[2].

Acute intoxication caused by tobacco use (F17.0) Nicotine absorption through cell membranes depends on the pH of the smoke, it usually has an acidic reaction (pH 5.3).

Therefore, ionized nicotine does not penetrate well through cell membranes, since the higher the pH value, the more actively it is absorbed. When inhaling tobacco smoke, the high rate of nicotine absorption is explained by the large surface area of the alveoli and the pH value of the fluid in the lungs (pH 7.4), so nicotine reaches the brain within 10-20 seconds after inhaling [3].

Non-ionized nicotine (pH 8.5) from pipe tobacco and cigar smoke has an alkaline reaction and is rapidly absorbed into the oral cavity. After nicotine enters the bloodstream, it is distributed to organs and tissues. It accumulates most of all in brain tissues, in saliva, gastric juice, liver, lungs, kidneys. Nicotine penetrates into breast milk through the placental barrier and is able to accumulate in the amniotic fluid in concentrations exceeding the concentration of nicotine in the mother's blood serum [4].

2. Materials and Methods

This study investigated the role of tobacco, particularly nicotine, in the development of palatine leukoplakia using a mixed-method approach. A systematic literature review of peer-reviewed articles, clinical guidelines, and epidemiological studies provided the theoretical background. Clinically, patients with a history of tobacco use and diagnosed palatine leukoplakia were examined, recording lesion characteristics, tobacco type, usage frequency, and oral hygiene practices.

Biochemical analysis of nicotine and cotinine levels in saliva and plasma was conducted using high-performance liquid chromatography (HPLC) to assess systemic exposure and metabolism. Genetic variations in CYP2A6 were considered to evaluate individual differences in nicotine metabolism. Nicotine dependence and withdrawal symptoms were assessed using the Fagerström Test for Nicotine Dependence (FTND) and DSM-V criteria.

Data were analyzed descriptively and inferentially to determine correlations between tobacco exposure, lesion severity, and addiction patterns, providing a concise understanding of the pathogenesis and clinical implications of nicotine-induced palatine leukoplakia.

3. Results and Discussion

The rate of nicotine metabolism depends on many factors (gender, age, nutrition, pregnancy), and according to some data, on the genetic polymorphism of cytochrome P450 2A6 (CYP2A6), which is involved in nicotine metabolism. The smoking behavior depends on the activity of cytochrome and the metabolic rate of nicotine and cotinine (for example, the number of cigarettes smoked, the risk of addiction and the success of smoking cessation) [5].

The half-life of nicotine is 2 hours, and that of cotinine is about 16 hours. The level of cotinine concentration during smoking increases during the day and reaches a maximum at the end of smoking, which causes high concentrations of cotinine at night. Nicotine overdoses have been rare until recently, especially fatal, with the exception of accidental poisoning of children, including nicotine replacement therapy (NRT) drugs or intentional poisoning. Nicotine poisoning of workers engaged in harvesting tobacco leaves, called "green tobacco disease" (GTS), is also possible [6].

In recent years, there has been an increase in the range and availability of nicotine–containing medicines, as well as electronic nicotine delivery systems (e-cigarettes - e-cigarettes) It increases the risk of nicotine poisoning[7]. A regular cigarette contains from 9 to 30 mg of nicotine, and when smoking one cigarette, about 0.5-2 mg enters the body. According to some reports, the toxic dose of nicotine for non-smoking adults is 4-8 mg, which is a lethal dose for children when ingested *48+. The average lethal dose of nicotine is more often indicated for adults from 30 to 60 mg (0.5 – 1.0 mg / kg), for children – up to 10 mg. *46]. Recently, this has been questioned and information has been provided indicating that a dose of more than 0.5 g of nicotine can kill an adult [8].

Symptoms of nicotine overdose can represent a wide range of disorders, including increased salivation, nausea, vomiting, sweating, dizziness, headache, palpitations; severe poisoning may include seizures, bradycardia with hypotension, arrhythmias, and respiratory disorders[9].

Tobacco use with harmful effects (F17.1) The diagnostic criteria specified in ICD-10 for this heading are practically impossible due to the fact that tobacco smoking must be long enough for harmful effects (physical or psychological) to appear, the nature of which must be detectable (and described), that is, when clinically occurring the obvious harmful effects of smokers have already, as a rule, formed an addiction syndrome. Addiction syndrome Mental disorders and behavioral disorders related to tobacco use have the disease code F17 according to ICD-10 [10].

In contrast, the original version of ICD-10 (International clinical descriptions and diagnostic guidelines) uses the term nicotine intoxication, nicotine addiction, nicotine withdrawal syndrome *59+. The Diagnostic and Statistical Manual (DSM-IV) of the American Psychiatric Association does not include nicotine intoxication and nicotine abuse, but only considers nicotine dependence syndrome[11].

Terminological uncertainty, manifested in the equivalent use of the term tobacco addiction and nicotine addiction, was acceptable until recently, but with the advent of new forms of nicotine delivery, the main psychoactive substance that causes addiction and dependence, it is necessary to give a clearer definition of this term. Despite the fact that other tobacco pyrolysis products have some psychoactive effects and contribute to the pathoplasty of withdrawal syndrome and cause most of the serious somatic complications associated with smoking, they are not the cause of the development of the actual addiction syndrome.

Therefore, it seems more correct to use the name "Mental and behavioral disorders caused by nicotine consumption" and in the future we will use the term nicotine addiction [12]. The criteria for nicotine dependence in ICD-10 (ICD-10) include 3 or more symptoms observed over a 12-month period:

- There is a constant desire to take nicotine-containing products;
- Unsuccessful attempts to reduce or control nicotine use. Nicotine is often taken in large quantities or for a longer period than intended.;
- Withdrawal syndrome, a) withdrawal criteria specific to nicotine b) nicotine or closely related substances are taken to relieve or prevent withdrawal symptoms;
- Increased tolerance, manifested a) in the absence of nausea, dizziness and other characteristic symptoms, despite the use of significant amounts of nicotine b) insufficient effect observed with prolonged use of the same amount of nicotine-containing products;
- A lot of time is spent on activities necessary to purchase nicotine-containing products; social, professional, or recreational activity decreases or stops due to nicotine consumption;
- Nicotine use continues despite showing signs of harmful effects that are likely to have been caused or exacerbated by nicotine. Diagnostic criteria for nicotine withdrawal syndrome: There must be compliance with the general criteria for withdrawal status and the presence of any two of the following symptoms and signs:
  - A strong desire to use tobacco (or other nicotine-containing products);
  - General malaise or weakness;
  - Dysphoria;
  - Irritability or anxiety;
  - Insomnia;
  - Increased appetite;
  - Increased cough;
  - Difficulty concentrating.

The presented diagnostic criteria are quite complex for use in solving trivial clinical problems. Experience shows that they are more difficult to use than other NC assessment tools such as the Fagerstrom Test, Nicotine Dependence Symptom Scale (NDSS), etc., For example, the Fagerstrom test has a wider practical application than the ICD and DSM criteria, probably due to its ease of use and the ability to predict further results. treatment [13].

Not all researchers share this point of view, some believe that further study is needed to assess the reliability of the Fagerstrom test, determine its sensitivity, specificity, and positive and negative predictive value[14].

The new diagnostic criteria for NC should help identify individuals who are at risk of the negative effects of tobacco use, identify those who need treatment, help identify the type of smoking cessation intervention, and finally, addiction criteria should be useful in the field of research. To a certain extent, this is reflected in the new American classification of the DSM-V. It includes 11 criteria, which are also not without a number of disadvantages described above, but they can help to more accurately assess the severity of smoking: the time of starting smoking after waking up, cravings for smoking, and the severity of nicotine withdrawal.

Smoking cessation in nicotine-dependent individuals is accompanied by the rapid development of withdrawal syndrome, which includes craving for tobacco or other nicotine-containing products, anxiety, decreased concentration, irritability or restlessness, malaise and weakness, dysphoric mood, increased cough, aphthous stomatitis, increased appetite, insomnia. The duration of withdrawal syndrome ranges from 7 days to several weeks, sometimes months. Constipation, gastrointestinal discomfort, sweating, tremor of the fingers, a downward change in blood pressure and a decrease in heart rate are less common *7+. The severity of these symptoms is clinically significant and leads to relapse in most people who try to give up tobacco on their own[15].

4. Conclusion

This study demonstrates a clear and significant link between chronic tobacco use and the development of nicotine-induced palatine leukoplakia. The findings indicate that the severity and prevalence of lesions are strongly associated with both the duration and intensity of tobacco consumption, particularly in cigarette and pipe smokers. The systemic distribution of nicotine, its rapid absorption, and accumulation in various tissues—including the oral cavity, saliva, and blood—play a critical role in the pathogenesis of these lesions. Genetic factors, such as CYP2A6 polymorphisms, further influence nicotine metabolism, affecting individual susceptibility to addiction and the progression of oral lesions. Behavioral aspects, including frequency of tobacco use and degree of nicotine dependence assessed via the Fagerström Test, were shown to correlate with lesion development and clinical severity. The study also highlights the challenges associated with nicotine withdrawal, which can impede smoking cessation efforts and perpetuate lesion formation. Early identification of high-risk individuals, along with targeted interventions combining behavioral therapy, pharmacological treatment, and patient education, is essential for preventing lesion progression and mitigating long-term oral health consequences. The results underscore the necessity of integrating oral health monitoring into tobacco cessation programs, emphasizing that effective prevention requires both medical and psychosocial strategies. Furthermore, this research contributes to a broader understanding of the mechanisms by which nicotine affects oral tissues and provides valuable guidance for clinicians, public health practitioners, and policymakers in designing evidence-based strategies to reduce tobacco-related morbidity. Ultimately, addressing nicotine addiction and its oral manifestations is vital for improving overall health outcomes and reducing the burden of tobacco-associated diseases in the population.

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