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КОНЦЕПЦИЯ СНИЖЕНИЯ ВРЕДА ОТ ТАБАКА: ПРОШЛОЕ, НАСТОЯЩЕЕ, БУДУЩЕЕ

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The Concept of Harm Reduction from Tobacco: Past, Present, Future

Резюме

Концепция «снижения вреда от табака» (СВОТ) является темой для дискуссии в контексте международной борьбы против употребления любых видов табака. Такая концепция предполагает предоставление потребляющим табак лицам, которые не могут или не желают прекратить табакокурение или потребление других видов табака (нюхательный, жевательный), менее вредную табачную продукцию с модифицированным риском (ТПМР) для дальнейшего употребления. Скептицизм в отношении СВОТ огромен и связан с негативным опытом табачных компаний по выпуску сигарет с низким содержанием табачных смол/никотина, которые должны были иметь существенно более низкие риски для здоровья чем обычные сигареты. Парадоксально, но именно такой опыт послужил трамплином к росту числа табачных изделий, которые потенциально обладают свойствами ТПМР. Более того, некоторые члены антитабачной коалиции, включая ВОЗ, рассматривают переход табакокурильщиков на ТПМР как стратегию с большим потенциалом. Однако, Европейская группа специалистов считает, что стратегия СВОТ не работает и приведёт к привыканию к табаку ещё одного поколения молодых лиц. В этой статье мы подвергли критическому анализу историю прошлого и настоящего табачных изделий, мифы и противоречия вокруг них. Мы постарались максимально объективно оценить современную концепцию СВОТ, обладающую высоким потенциалом к реальному сокращению числа смертей, связанных с табакокурением.

Ключевые слова: *снижение вреда от табака, СВОТ, табачная продукция с модифицированным риском, ТПМР, табакокурение*

Конфликт интересов

Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

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Abstract

The concept of tobacco harm reduction (THR) is a speculative and controversial topic in the context of the international battle against the use of all types of tobacco. This concept involves providing tobacco users who are unable or unwilling to quit smoking or using other types of tobacco (snuff, chewing), with modified risk tobacco product (MRTP) for continued use. Skepticism about THR is huge and is associated with the negative experience of tobacco companies to produce cigarettes with a low content of tobacco tar/nicotine, which should have had significantly lower health risks than conventional cigarettes. Paradoxically, such an experience served as a springboard to an increase in the number of tobacco products that potentially have the properties of MRTP. Moreover, some members of the anti-smoking coalition, including WHO, consider the transition of tobacco smokers to MRTP as a strategy with great potential. However, the European Group of Experts believes that the MRTP strategy does not work and will lead to

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another generation of young people getting used to tobacco. In this article, we have critically analyzed the history of the past and present of tobacco products, myths and contradictions around them. We have tried to evaluate the modern concept of S THR as objectively as possible, which has a high potential for a real reduction in the number of deaths associated with smoking.

Key words: *tobacco harm reduction, THR, modified risk tobacco product, MRTP, tobacco smoking*

Conflict of interests

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ENDS — efficiency of Electronic Nicotine Delivery Systems, ERS — European Respiratory Society, FCTC — World Health Organization Framework Convention on Tobacco Control, FDA — Food and Drug Administration, MRTP — Modified Risk Tobacco Products, PMTA — premarket tobacco product application, THR — tobacco harm reduction, THS — tobacco heating system

Introduction

Today, there are about 1.3 billion tobacco smokers on our planet; six million of them die annually from smoking cigarettes and other combustible tobacco substances. Just in the USA, such a "tobacco landscape" causes 480,000 deaths a year, results in 16 million cases of tobacco-related diseases, and reduces the life expectancy of smokers by ten years [1, 2]. Moreover, the analysis of the current "tobacco scenario" revealed that the high costs (disease burden) due to tobacco-related deaths and diseases can be significantly reduced by implementing measures to stop widespread tobacco smoking [3]. There are effective tobacco control strategies, such as raising prices of cigarettes and tobacco products in general, anti-smoking awareness campaigns in media, smoking bans in public places and at work, and providing affordable evidence-based medical methods of quitting smoking. Such measures have contributed to a significant and consistent reduction in cigarette smoking. Nevertheless, the role and significance of such programs in "reducing the harm from tobacco and burned tobacco products" is still the subject of numerous discussions [4].

It is worth reminding that the "tobacco harm reduction" (THR) concept provides for "minimizing harm, overall mortality and morbidity among tobacco smokers without completely quitting tobacco and nicotine use" [5]. This means that THR recognizes tobacco smoking cessation/abstinence as a "required and achievable outcome", leaving a "window of opportunity" for alternative harm reduction for patients who would never be able to quit tobacco smoking. Moreover, THR has no advantages or precedence over complete cessation/abstinence from tobacco use. In fact, the THR concept is aimed at respecting certain human rights when patients with tobacco dependence are provided with modified risk tobacco products (MRTP) [5, 6]. THR is rather a measure of social justice that potentially eliminates medical and social inequalities between healthy and tobacco-dependent individuals. For example, tobacco dependence among people "below the poverty level" or with a low level of education is many times higher than among the general population [7]. This social group (poverty) smokes more often, has high tobacco dependence, and more often makes an attempt to quit smoking with an extremely low chance of success. This social group has a higher risk of developing lung cancer compared to individuals with high income and education. A similar scenario is observed among tobacco smokers with mental illnesses and type 2 diabetes mellitus (DM2) [8].

Considering the high prevalence of tobacco smoking and the practical difficulties in achieving complete tobacco cessation, access to MRTP for tobacco-dependent patients may be an alternative strategy to reduce the risks of health deterioration. However, the role of THR in tobacco control is poorly understood, controversial and disputable. In this analytical review, we tried to analyze the history of the past and present of tobacco products, present-day THR concepts, myths and contradictions around them, as well as the most promising approaches to implementing this concept for tobacco-dependent patients with a high potential for actual reduction of the number of smoking-related deaths.

1. Evolution of Risk Modified Tobacco Products

Much skepticism about the THR concept is fueled by negative experiences with low tar/nicotine cigarettes. In 1964, after the publication of an official medical report about the link between tobacco smoking and a number of fatal diseases, for the first time, serious concerns arose among different social groups (rich and poor) regarding health risks [9]. At the same time, cigarette manufacturers demonstrated a genuine interest in "safe cigarettes".

Moreover, an academic paper was published on the toxicity of cigarettes and the relationship between tar/nicotine levels and the number of cigarettes smoked with the development of malignant tumors/lung cancer [10]. These studies revealed that the health risk for a smoker will be significantly reduced if there is less tar and nicotine in cigarettes. Subsequently, the US Federal Chamber of Commerce approved testing of tar/nicotine levels in cigarettes using "smoking machines" with "standardized smoking parameters". Later, many tobacco companies started producing and extensively selling cigarettes with low tar and nicotine. It is hard to believe that health conscious tobacco smokers were advised to switch to "special cigarettes" rather than quit smoking! [11]. The tag lines of that time were: "SMOKE IT PROPERLY: JUST LIGHT CIGARETTES!"; smokers were portrayed as athletic, cheerful people in nice scenery with excellent health. Also, "SPECIAL CIGARETTES" were designated as "light", "ultralight", "soft", "zero" [12].

With the accumulation of scientific knowledge about tobacco-related health risks, the myth that cigarettes with low tar/nicotine content can reduce the risks of cancer and death among tobacco smokers compared to "conventional" cigarettes has been finally dispelled. It was found that the reduction of tar/nicotine, as measured by "smoking machines", was achieved only by the design of cigarettes, not by an actual reduction in tar/nicotine in the tobacco filler. For example, additional ventilation of the cigarette filter and adding special smoke vents are now the primary methods of reducing the "tobacco load" [13]. However, these "ventilated filters" have changed the behavior of smokers by developing a new "compensatory smoking technique". In fact, it made it possible to achieve high levels of "tobacco exposure" by increasing the puff time, blocking ventilation openings at the moment of inhalation and puffing, and also by increasing the number of cigarettes smoked per day [14]. As a result, the expected reduction in health risks to smokers did not correlate with that calculated by "smoking machines" [15]. It is possible that it was the "ventilated filters" of cigarettes that contributed to the increase in cases of peripheral lung cancer (adenocarcinoma) due to deep inhalation of toxic chemicals by the smoker and/or increased mutagenicity of tobacco smoke due to the specific features of the combustion of cigarettes with a ventilated filter [16].

A huge scandal erupted in 2006 when the US Department of Justice prosecuted a number of tobacco companies for racketeering and fraud. In her final opinion, Judge Gladys Kessler said that the tobacco companies were deliberately deceiving the public. The court found that, for decades, tobacco companies had been producing cigarettes with low tar/nicotine content, knowing that "light", "ultralight", "soft", and "zero" brought no health benefits to smokers compared to standard cigarettes. Nevertheless, they made smokers believe that these very cigarettes were a way of reducing the adverse health effects of smoking. Therefore, they could be an alternative to complete cessation/abstinence from tobacco smoking [17]. Later, the US Federal Chamber of Commerce (2008) completely removed tar/nicotine labeling on cigarette packs that could mislead smokers. Finally, in 2010, the Food and Drug Administration (FDA), in accordance with the Family Smoking Prevention and Tobacco Control Act (FSPTCA), banned the use of low-risk smoker labels on cigarette packs or in advertisements, including "light", "ultralight", "mild", "zero". Nevertheless, tobacco companies still use colors (e.g., silver, gold) to denote the particular delicacy of products, as well as the terms "thin" or "soft" that support the misconceptions about their low harm to the health of smokers [18].

In the context of THR, the publication by Prof. Michael Russell (UK) is of interest. It calls for reducing tar content in cigarettes but maintaining a moderate nicotine level. According to Michael Russell, "People smoke for nicotine and die from the tar. Moreover, as long as there is a sufficient amount of nicotine in the "cigarette puff", smokers will be able to easily tolerate the reduction to zero of any other harmful components" [19]. In a series of experiments, this approach relieved tobacco addicts from cigarettes and contributed to the cessation of tobacco smoking [20]. This "simple idea" was picked up in the 1990s by a number of tobacco companies targeting tobacco smokers with high health concerns through the provision of specialty products with potential harm reduction. These include: "premium taste" cigarettes with a "reduced level of carcinogens" and high level of nicotine; cigarettes with a "reduced level of nicotine" and zero nicotine cigarettes for "nicotine freedom"; and a variety of non-combustible tobacco systems. It is obvious that such tobacco products do not in any way reduce harm to the health of tobacco-dependent patients [16].

There is an interesting report published in Sweden (1994) on the reduction of harm to people who use snus. SNUS is a special type of unburned tobacco product in the form of a small bag with shredded and moist tobacco to be placed between the upper lip and gum for a long time (30–60 min). Nicotine from tobacco is absorbed/enters the body through the oral cavity. Harm reduction has been associated with low tobacco-specific nitrosamines (TSNA) and other toxic/harmful substances in snus [21]. The study demonstrated that among Swedish men who use snus, there is a sharp decrease in cigarette smoking and a decrease in the incidence of lung cancer and myocardial infarction. Also, the rate of return to cigarette smoking among snus users is significantly lower than among those who quit smoking [22]. Compared

to EU other countries, Sweden, which banned "tobacco burning", currently has the lowest incidence of tobacco-related diseases. However, the European Commission for Tobacco Control is seriously concerned that overall tobacco use remains high in Sweden and that SNUS cannot be considered a "safe tobacco product" [23]. The "Swedish experience" led cigarette manufacturers in the United States to start selling SNUS products (for example, Camel Snus®, Marlboro Snus®) as a substitute for cigarettes in places where smoking is prohibited or as a means of quitting smoking. For example, an advertisement for "Camel Snus®" included the following headings: "Freeze Fire", "Deceive the Old Flame", "New York City Smokers: Rise Above Prohibitions!" or "Friends Bar" [24].

2. Reducing Tobacco Harm: Risks, Benefits, Acceptability

In accordance with US law (FSPTCA, 2009), the main regulatory authority for standard cigarettes, smokeless tobacco, and alternative tobacco products is the FDA, which is the main regulator of THR in the world today. It should be noted that the emergence of new tobacco products with different levels of risk of harm to the health of tobacco smokers is more likely due to the desire of tobacco companies to remain on the market than their actual desire to improve the THR concept [3]. For example, the widespread adoption of "electronic cigarettes" created a break between those who perceived the technology as having the potential to replace traditional cigarettes and those who recognized it as even more harmful than cigarettes. Also, in 2013–2014, there was a public debate over an evidence-based plan for tobacco control that maximizes the benefits and minimizes harm to public health. Despite the consensus reached regarding the risks of various nicotine delivery systems to human health, the main question remained unanswered. The question was represented like this: "Should we save the millions of lives of tobacco dependent patients (who cannot stop using tobacco) or those who do not want to stop using tobacco by switching to modified risk tobacco products (MRTP), or fighting to prevent a new generation of nicotine addiction through an absolute ban on the use tobacco in any form?" (Fig. 1) [25].

Medical experts who favor absolute and total prohibition of using tobacco in any form express serious fears and concerns that MRTP and electronic cigarettes (e-cigarettes) can drive up the use of harmful substances by young people. According to the "gateway theory", this may discourage tobacco-dependent patients from trying to quit tobacco use. Their concerns were not unfounded. Studies carried out over the years revealed extremely contradictory data regarding the effectiveness of electronic nicotine delivery systems (ENDS) as a means of completely quitting smoking [6, 14]. However, the FDA has approved a global nicotine and tobacco regulatory plan to switch tobacco-dependent patients to MRTP as an additional strategy to improve public health [26].

However, the position of the FDA (2019), as the regulator of THR, on the one hand, provides for the abolition of restrictions regarding ENDS with cartridges without menthol/tobacco and discrimination against flavored cartridges. On the other hand, it requires focusing on preventing young people from accessing such products and their promotion among young people. The ban does not apply to ENDS that contain no fruit flavors, if there is no promotion of their use among young people. This allows adult tobacco-addicted patients who wish to quit smoking to use flavored e-cigarettes more efficiently. According to the US Secretary of Health and Human Services, Alex Azar, "Priority should be given to preventing young people from accessing ENDS with the right balance of using e-cigarettes by adults in order to quit smoking. All rules should be followed to ensure that ENDS do not lead to the development of "nicotine dependence" in our youth" [28].

At the same time, a group of experts from the European Respiratory Society (ERS) argue that the use of ENDS (electronic cigarettes) increases the number of patients with severe lung diseases by 1,600 cases/year, with 34 cases of being fatal. The Tobacco Control Committee of the ERS Consumer Protection Council published a paper that included seven of the main arguments of the ERS about the failure of the THR concept as a public tobacco control measure [29]. Let's consider them in more detail.

Figure 1. *Schematic representation of the main dilemma of the tobacco harm reduction concept (THR). The explanation is in the text. (Adapted from: Hatsukami DK et al. Prev Med. 2020 Nov; 140: 106099)*

Argument 1. THR strategy is based on the erroneous assertion that tobacco smokers are unable or unwilling to quit tobacco use. On the contrary, most of them do not want to be addicted to nicotine and want to stop smoking. Present-day tobacco smokers smoke fewer cigarettes, are more motivated to quit smoking, and are less tobacco-dependent than in the past. Moreover, there is safe and effective medical treatment for tobacco dependence [30].

Argument 2. THR strategy is based on poorly documented evidence that ENDS are highly effective in smoking cessation. It has been proven that 80% of people who quit smoking by switching to electronic cigarettes remain addicted to nicotine. Also, long-term use of ENDS (more than three months) reduces the patients' chance of abstaining from nicotine. Studies of smokeless tobacco as a cessation agent are controversial and revealed no convincing effects [31].

Argument 3. THR strategy is based on the erroneous assumption that tobacco smokers will completely stop smoking conventional cigarettes and switch to MRTP. It has been proven that 80% of patients who switch to electronic cigarettes continue to smoke conventional cigarettes. In addition, there are no reliable data on a significant reduction in their smoking of conventional cigarettes. Moreover, "double tobacco use" is becoming more common among tobacco-dependent patients who switch to smokeless tobacco, which causes double harm to the health of such patients [22].

Argument 4. THR strategy is based on poorly documented evidence of low harm and safety of ENDS. There is currently no proof of the safety of ENDS. On the contrary, a series of independent studies revealed their potential harm. For example, e-cigarette aerosols can cause acute endothelial vascular dysfunction and reactive oxidative stress. Short-term inhalations through ENDS systems causes airway obstruction and disrupt normal pulmonary homeostasis. Vape (cloud, vapor) of electronic cigarettes causes coughing and wheezing and can trigger suffocation and a bronchial asthma attack [32].

Argument 5. Even if ENDS at first glance seem less harmful than conventional cigarettes, they have an absolutely negative effect on public health. When assessing the pros and cons of the widespread use of ENDS, it is important to correctly consider their impact on all groups of the population, not only on a small group of tobacco smokers. Overall, considering this issue from the perspective of public health, ENDS potentially lead the new generation (youth), previously involved in tobacco smoking, to nicotine use, especially children and adolescents who like electronic cigarettes with candy or fruit flavors. Research has shown that there is a significant increase in the risk of early smoking and the chances of returning to traditional cigarettes among e-cigarette users. In this context, smokeless tobacco use significantly increases the possibility of switching to traditional cigarettes [33].

Argument 6. Tobacco smokers consider ENDS a viable medical alternative to tobacco quitting, which is wrong. This is why they abandon professional approaches and proven pharmacological treatments, which increases the number of failed cessation attempts and compromises the effectiveness of tobacco dependence therapy [34].

Argument 7. THR strategy is based on the erroneous claim that the "tobacco epidemic" cannot be controlled. On the contrary, the greatest success of modern-day public health is a significant reduction in the number of tobacco smokers due to tobacco bans. Countries with active control and bans on tobacco use have seen a significant and rapid decline in the prevalence of tobacco smokers and tobacco use in general [1, 35].

What is the conclusion made by the group of experts of the European Respiratory Society?

First, the THR concept is based on good intention (design) and poorly documented facts and assumptions. Human lungs are designed to breathe "clean air", not "reduced levels of toxins and carcinogens", and the human body should not be addicted to drugs, nicotine, tobacco. That is why more than 40 European countries have banned all ENDS [29].

Second, the ERS cannot recommend any modified product that is harmful to human health or lungs. This is why the ERS strongly supports the World Health Organization Framework Convention on Tobacco Control (FCTC), a treaty accepted by the World Health Organization (WHO) in response to the globalization of the tobacco epidemic, which regulates all types of tobacco products [29].

Third, at present, the ERS does not consider the THR concept as an alternative to the strategy of complete cessation of tobacco use, even for tobacco-dependent patients, as the main doctrine of improving public health [29].

3. Reducing Tobacco Harm: Current Perspective

Despite the differences in FDA and ERS approaches to tobacco harm reduction (THR), the THR concept has a right to life as a measure of social justice for nicotine and tobacco addicted patients (who cannot quit smoking) who experience the greatest medical and

social inequality. Switching them to modern high-tech products with a reduced nicotine and tar content, and tobacco combustion products opens a real "window of opportunity" in preserving their life span [36]. For example, switching tobacco smokers with more than ten years of experience to cigarettes with low and extremely low nicotine content halved the number of cigarettes smoked, reduced "tobacco dependence", exposure to toxic/carcinogenic substances, and doubled the number of attempts to quitting smoking [37]. However, a reduced nicotine level in cigarettes did not correlate with changes in mood, depression, and the frequency of alcohol and cannabinoid use in these patients. Moreover, the strategy of drastically reducing nicotine in cigarettes versus stepwise reduction (nicotine replacement therapy) inevitably leads to an increase in the number of people looking for it in other sources. These consequences and the low efficacy of low-nicotine products in encouraging tobacco-dependent patients to quit smoking deprives them of any prospects in the THR concept [38].

It should be noted that there are other innovative products that have passed the premarket tobacco product application (PMTA) and FDA-approved innovative products that can be used without burning tobacco ("unburned tobacco"): General Snus (Swedish Match) and IQOS (Phillip Morris International, PMI). Randomized clinical trials (RCTs) revealed that General Snus had lower levels of tobacco-specific nitrosamines (TSNAs) and other toxic substances compared to other brands of smokeless tobacco products. However, the very concept of SNUS/smokeless tobacco has not gained acceptance among smokers [3, 22, 25, 39].

Another product in the category of "unburned tobacco" is the tobacco heating system (THS) designed to evaporate nicotine from a special "tobacco stick" [40]. Its important difference from conventional cigarettes is that there is no combustion of tobacco and tobacco smoke, which means that the following gaseous components are not produced: carbon monoxide and carbon dioxide, hydrogen cyanide, ammonium, isoprene, acetaldehyde, acrolein, nitrobenzene, acetone, hydrogen sulfide, hydrocyanic acid and other hazardous substances. This reduces the aerosol cloud of all substances that are hazardous to the patient's health by 90–95%. For comparison: aerosol cloud during tobacco burning contains solid particles and tar, 50% glycerin and water, has more than 4,000 different chemical compounds, including more than 40 dangerous carcinogenic substances and at least 12 substances that cause cancer [41].

There are important RCTs that have been carried out to investigate the "toxicity" of THS aerosol to smokers. It has been proven that the aerosol produced by the THS system is ten times less dangerous than cigarette smoke in terms of triggering the mechanisms of atherosclerosis, premature cellular aging, endothelial dysfunction that play a major role in the development of cardiovascular diseases (Fig. 2) [42].

The practical interest of the applicability of THS systems in tobacco-dependent patients has been studied in large-scale RCTs conducted among patients from different countries, different ethnic groups and cultural traditions. For example, there was an interesting six-month multicenter RCT, further extended to 12 months, in healthy adult smokers with two parallel groups: 1) individuals who had switched to THS systems; 2) individuals who had completely stopped smoking. The potential of THS systems to influence eight key pathogenetic mechanisms of disease formation (inflammation, oxidative stress, lipid metabolism, blood clotting, endothelial function, pulmonary function, genotoxicity) was studied in comparison with patients who had completely stopped smoking. A total of 2,556 tobacco smokers were screened and 1,795 tobacco smokers were enrolled; 984 of them were randomized into three groups (traditional cigarettes n = 496; THS n = 488; quit smoking n = 811). A representative group and extension of the study to 12 months allowed to study clinically important long-term results of the THS system (Fig. 3) [43, 44]. The primary points of observation were the markers of disease development: 1) lipid metabolism — HDL-C (high density lipoproteins); 2) blood clotting — 11-DTX-B2 (11-dehydrothromboxane B2); 3) endothelial function — slCAM-1 (soluble intercellular adhesion molecule-1); 4) acute effects — COHb (carboxyhemoglobin); 5) inflammation — WBC (leukocytes); 6) oxidative stress — 8-epi-PGF2 (8-epi-prostaglandin F2 alpha); 7) pulmonary function — FEV1%pred (forced expiratory volume in 1 second from the due values); 8) genotoxicity — Total NNAL (total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol).

Secondary observation points were the components of tobacco aerosol: 1) carbon monoxide (CO) in exhaled air; 2) monohydroxy butenyl mercapturic acid (MHBMA); 3) 3-hydroxypropyl mercapturic acid (3-HPMA); 4) total N-nitrosonornicotine (Total NNN); 5) 2-cyanoethyl mercapturic acid (CEMA); 6) 3-hydroxybenzo(a)pyrene (3-OH-B[a]P); 7) 3-hydroxy-1-methylpropyl-mercapturic acid (3-HMPMA); total 1-hydroxypyrene (Total 1-OHP). To describe the effects of nicotine, in addition to plasma levels of nicotine and cotinine, nicotine equivalents (NEQ) were determined as the molar sum of free nicotine, nicotine glucuronide, free cotinine, cotinine glucuronide and free trans-30-hydroxycotinine and trans-30-hydroxycotinine-glucuronide in urine (expressed as concentration adjusted for creatinine).

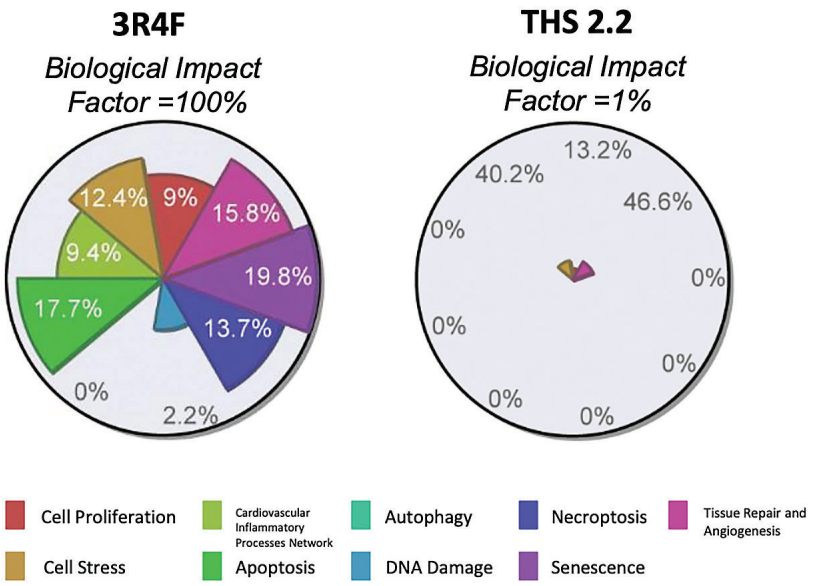

Figure 2. *Graphical representation of the study of the aerosol THS for toxicity in comparison with the smoke of a conventional cigarette (3R4F). The explanation is in the text. (Adapted from: Poussin C et al. Toxicology. 2016 Jan 2; 339: 73-86)*

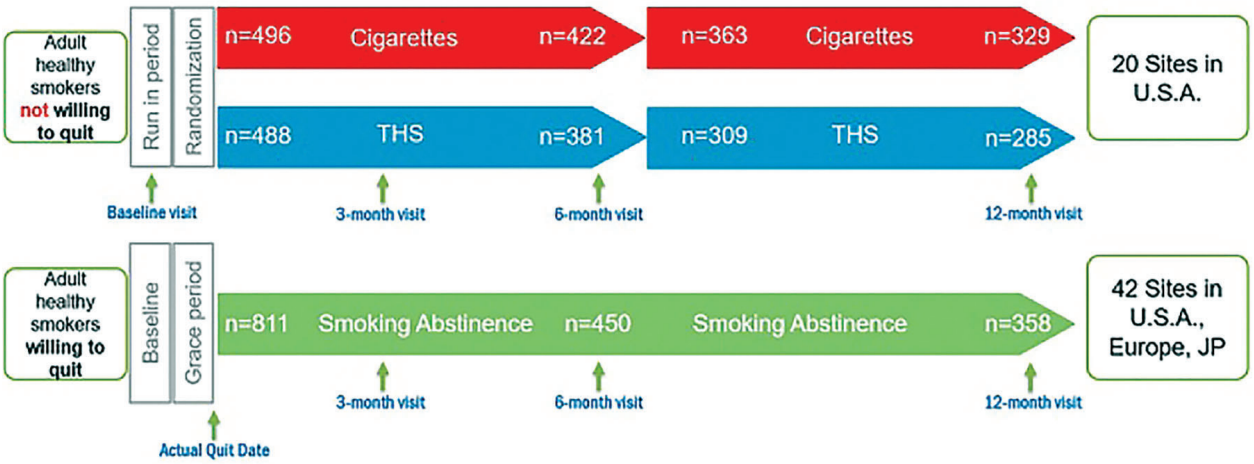

Figure 3. *Graphical representation of the design of a 12-month RCT. The explanation is in the text. (Adapted from: Ansari SM et al. JMIR Res Protoc. 2018 Aug 24;7(8):e11294).*

Results of this study demonstrated that all values of the endpoints of the main observation group (THS group) improved similarly to the values of the smoking cessation group. Moreover, five out of eight markers of inflammation development had statistically significant ($p < 0.05$) positive changes in comparison with the group of continuing smoking (traditional cigarette group) and were similar to those in the smoking cessation group (Table 1) [44].

All components of the "tobacco aerosol" were significantly reduced in the THS group compared to cigarette smokers, while there was no difference between the groups in nicotine exposure (NEQ) (Fig. 4) [44].

This study convincingly demonstrates the positive effects of the strategy of switching tobacco-dependent patients to THS systems. First, it demonstrated a statistically significant improvement in five of the eight major markers of inflammation development to the level observed only during smoking cessation. At the same time, these patients retained the level/dose of nicotine and subjective effects similar to those in the group of active tobacco smokers. This can be an important argument that THS systems can be a feasible alternative for tobacco-dependent patients. It is important that the positive biological effects in patients of the THS

group lead to a significantly lower health risk than continuing smoking. Using THS systems in tobacco-dependent patients in accordance with the THR concept is highly speculative. However, it is very promising with further improvement of "unburned tobacco" technology [45].

Another large-scale study by P.N. Lee et al. (2018) assessed the health effects of modified risk tobacco products (MRTP) on the health of the Japanese population by creating simulation models over a 20-year period starting from 1990. It was found that the overall decrease in the number of deaths from lung cancer, coronary heart disease, stroke, chronic obstructive pulmonary disease due to tobacco smoking among men/ women for 20 years amounted to 269,916 cases; with the complete cessation of tobacco smoking at the baseline. The decrease in the number of deaths ranged from 167,041 to 232,519 cases, if at baseline patients switched to MRTP systems (switching level is equivalent to 70–90% of complete cessation of smoking) [46].

In a meta-analysis, A. Ratajczak et al. (2020) included 15 RCTs from Cochrane, PubMed and Embase on acceptability, awareness, and patient switch to IQOS® MRTP. Results varied greatly due to smoking status: among young smokers, there was a high interest in the "heating tobacco" system. On the other hand, there was a similar interest in THS systems among nonsmokers, indicating the emergence of new tobacco users. Overall susceptibility/readiness to use IQOS was higher (25.1%) than among traditional cigarettes (19.3%) and lower than among e-cigarette users (29.1%). The authors concluded that THS systems could potentially be categorized as modified risk tobacco products considering their impact on chronic diseases traditionally associated with tobacco smoking. However, further large-scale studies are required to verify this potential [47].

Table 1. *Dynamics of markers of inflammation development*

Endpoint	Effect	96.875 % CI	P value
HDL-C (mg/dL)	3.09	[1.10; 5.09]	<0.001
WBC count (GI/L)	-0.420	[-0.717; -0.123]	0.001
sICAM-1 (%)	2.86 %	[-0.426; 6.04]	0.030
11-DTX-B2 (%)	4.74 %	[-7.50; 15.6]	0.193
8-epi-PGF2a (%)	6.80 %	[-0.216; 13.3]	0.018
COHb (%)	32.2 %	[24.5; 39.0]	<0.001
FEV1 %pred (post-bronchodil.)	1.28 %	[0.145; 2.42]	0.008
Total NNAL (%)	43.5 %	[33.7; 51.9]	<0.001

Note: Adapted from: Lüdicke F et al. Cancer Epidemiol Biomarkers Prev. 2019 Nov; 28(11): 1934-1943

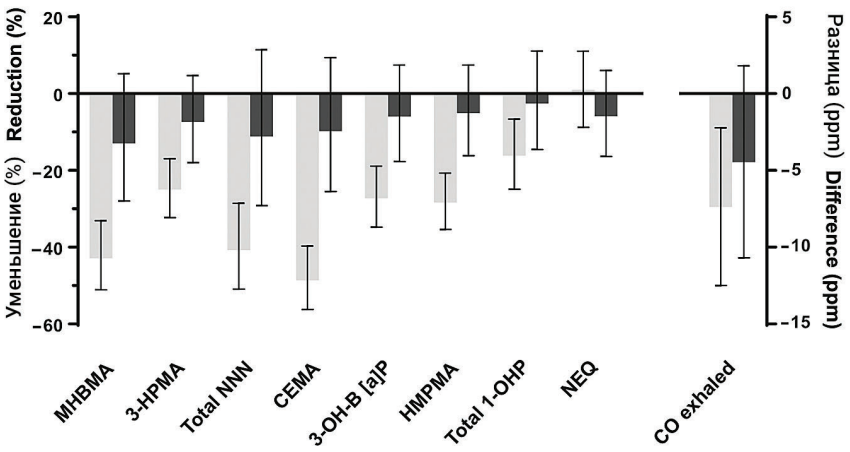

Figure 4. *Dynamics of reduction of toxic components of "tobacco aerosol" in the group of THS users (light gray) compared to the group of tobacco smokers (dark gray). The explanation is in the text. (Adapted from: Lüdicke F et al. Cancer Epidemiol Biomarkers Prev. 2019 Nov;28(11):1934-1943).*

4. Conclusion

Currently, there is considerable experience in the production and consumption of tobacco products with low tar/nicotine content, as well as knowledge and tools for the regulation of modified risk tobacco products (MRTP) for tobacco smokers with tobacco dependence or with no interest in quitting nicotine use [18]. There remains a fundamental disagreement over the benefits and risks of tobacco cessation/ abstinence and MRTP use for adult tobacco addicts. Obviously, the quickest way to reduce mortality and tobacco-related diseases is to "devalue" traditional cigarettes and other "burned tobacco" products by reducing their nicotine content to the minimum level of addiction [3]. Obviously, unburned tobacco products should also be tightly regulated in terms of toxicity, attractiveness, marketing and promotion in order to minimize their consumption by young people. On the other hand, adult tobacco-dependent patients should have a real opportunity to switch to MRTP [6, 17].

Today, the implementation of new pharmacological innovations in nicotine replacement therapy (NRT) provides real access to effective and well-known tools for the cessation of tobacco use [23]. It is NRT that has good potential to: 1) quickly eliminate "burned tobacco" from the market; 2) eliminate concerns about "unburned tobacco" products; 3) reduce the "double use" of tobacco products; 4) minimize the consumption of "burned tobacco" products among young people; 5) ensure the public that unburned tobacco products are MRTP products; 6) provide tobacco smokers and consumers of other forms of tobacco products with effective agents for nicotine addiction [25].

It is important that the "tobacco harm reduction" (THR) concept provides for "minimizing harm, overall mortality and morbidity among tobacco smokers without completely quitting tobacco and nicotine use" [5]. In fact, THR recognizes giving up/abstaining from tobacco as a required and achievable result, leaving a "window of opportunity" for tobacco-dependent (nicotine-dependent) patients to receive real help in maintaining their health while maintaining social justice measures, potentially eliminating medical and social inequalities between healthy and tobacco dependent individuals. Disputes and contradictions between the "Anglo-Saxon" and "European" views on the possibility of implementing THR can only be resolved through a global dialog [25]. In this context, unburned tobacco (THS) systems can be an acceptable alternative for tobacco-dependent patients. Of course, using THS systems in tobacco-dependent patients in accordance with the THR concept is highly speculative. However, it is promising with the further improvement of "unburned tobacco" technology [45–47].

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