REVIEW ARTICLE

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Impact of heated tobacco products on health – a comparative analysis with traditional cigarettes

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Abstract

Introduction. Smoking is one of the most significant modifiable risk factors for many diseases and related deaths. In recent years, more and more people are seeking alternatives that allow them to quit smoking and improve their quality of life. One such alternative is Heat-Not-Burn Tobacco Products (HTPs), which have gained significant popularity among both smokers and non-smokers. Their impact on human health has not yet been thoroughly investigated. This review summarizes the current knowledge regarding the impact of these devices on human health.

Objective. The aim of the study is to investigate the physiological and biochemical effects of HTP devices on human health, and to compare their impact relative to traditional cigarettes on the functions of the cardiovascular, respiratory, digestive, skeletal and urinary systems, oxidative stress, inflammatory state, and periodontal diseases.

Review Methods. A review was performed of studies available on PubMed and Google Scholar.

Summary. The scientific research cited in the review confirms the negative impact of HTP devices on human health, although clearly demonstrating that they represent a better alternative to traditional cigarettes. This is achieved through the reduction of harmful substance content in the inhaled aerosol, resulting in lower oxidative stress, inflammatory state, and intensity of many diseases affecting smokers.

Key words

inflammation markers, respiratory function, cardiovascular health, heated tobacco products, oxidative stress, traditional cigarettes, IQOS®

Abbreviations

HTP- heated tobacco product CC- combustible cigarette COPD- chronic obstructive pulmonary disease HDL-C- high-density lipoprotein

INTRODUCTION

Tobacco smoking represents one of the most significant public health threats worldwide, being a major modifiable risk factor for numerous chronic diseases and associated mortality, and has been extensively studied for its impact on human health. As early as the 19th century, initial scientific research suggested a link between cigarette smoking and various illnesses, but true advancements in this field did not occurr until the 20th century [1]. In the 1950s and 1960s, seminal studies by researchers such as Richard Doll and Bradford Hill provided ground-breaking evidence of a strong association between smoking and the risk of lung cancer [2]. Subsequent research confirmed that tobacco smoking is also a risk factor for many other diseases, including cardiovascular and respiratory diseases, cancers, strokes, oral diseases, urinary tract diseases, and bone diseases [3,4,5]. As research progressed, an increasing number of scientific papers documented the wide range of health issues associated with smoking. Additionally, epidemiological studies provided data on the impact of passive smoking on the carcinogenicity, respiratory, and cardiovascular systems of non-smokers, further emphasizing the importance of public anti-smoking campaigns and the implementation of restrictive smoking regulations in public places [6].

In recent years, there has been growing attention to exploring alternative methods of nicotine delivery that could reduce the harmful health effects associated with traditional

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cigarette smoking. One such innovative technology involves heated tobacco products (HTPs), with IQOS®, developed by Philip Morris International, as one of the most popular examples [7]. In HTPs devices, such as IQOS®, Glo, etc., tobacco-filled sticks are heated to a temperature of 350 °C using a heating metal blade or sheet and induction technology, resulting in the user inhaling an aerosol, not tobacco smoke as with traditional cigarettes, where the tobacco is completely burned at temperatures of around 700–950 °C [8]. Numerous studies have clearly shown that as a result, fewer toxic and carcinogenic substances are released during the use of HTPs [9]. Reductions in the emission of compounds such as acetaldehyde, formaldehyde and acrolein reach up to 80–96%. The most significant decrease was observed for styrene, toluene, benzene, toluene, isoprene, and 1,3-butadiene, reaching up to 99.8% (Tab. 1). Importantly, nicotine levels were almost the same when comparing HTPs sticks and CC, making HTP sticks a viable alternative for individuals addicted to nicotine [10].

Table 1.

Chemical substance	Reduction (%)[1]
Nicotine	0
NFDPM[2]	0
Acetaldehyde	80.5–88.2
Formaldehyde	82.9–96.2
1,3-Butadiene	99.7–99.8
Benzene	98.8–99.4
Isoprene	99.6–99.8
Styrene	96.9–98.6
Toluene	97.6–98.8

[1] reduction of emissions of specific substances in HTPs sticks compared to CC
[2] nicotine-free-dried particulate matter

Similar results were obtained by researchers from Japan, confirming that nicotine concentrations in IQOS® sticks and in the main aerosol are almost the same as in CC. Substances such as carbon monoxide (CO) and tobacco-specific nitrosamines (TSNAs) were also examined. Although IQOS® generated significantly lower levels of TSNAs and CO, these devices are still not entirely free from toxic compounds [11].

The advantages of HTP products over traditional cigarettes and electronic cigarettes were also described by Giuseppe Biondi-Zoccai et al., indicating reduced endothelial dysfunction and a smaller increase in Nox-2 protein, which is a marker of oxidative stress, during the use of these alternative devices [12].

Despite the positive aspects for individuals who have switched from CC to HTPs, it is worth noting that the availability, lack of nuisance smoke, and convenience of using such devices, have led to their uptake by younger individuals and those who had not previously used tobacco products. Among IQOS® users in Italy, almost half of them had not previously been regular cigarette smokers [13]. Additionally, it has been shown that despite promising results regarding cigarette smoking reduction, as many as 80% of participants were unable to completely replace cigarettes with IQOS® products within two weeks, resulting in the dual use of both products. Despite the significant increase in recent decades in societal awareness of the harmful effects of smoking, the number of smokers worldwide remains high, and in some age groups it has even increased, with tobacco smoking remaining a major public health risk factor [14, 15].

An important issue that garners interest among scientists, the medical community, and users alike, is the assessment of the impact of IQOS® devices on health. Despite claims by the manufacturers of reduced harm compared to traditional cigarettes, there is a need for comprehensive scientific research to evaluate the actual impact of these devices on the health of users.

OBJECTIVE

The aim of this scientific review is to assess existing studies and analyze data regarding the impact of IQOS® devices on health, with the ofcus on assessing potential health benefits and risks associated with the use of IQOS®, compared to smoking traditional cigarettes. Through the analysis of available scientific evidence, an attempt is made to provide an objective assessment of the risks associated with the use of HTPs devices, and additionally to provide recommendations regarding their potential impact on public health.

Cardiovascular system. In a study conducted by Gustaf Lyytinen et al., involving 23 young participants, exposure to HTPs was observed to lead to temporary increases in arterial stiffness, measured as pulse wave velocity (PWV) and augmentation index (AIx75). Both these parameters are considered important indicators of vascular function and are associated with an increased risk of cardiovascular diseases. Measurements were taken at baseline, and after 20 and 90 minutes. An increase in arterial stiffness was observed after exposure to HTPs, resulting from the short-term effects of nicotine, which can lead to activation of the sympathetic nervous system and disturbances in nitric oxide production by vascular endothelium. Additionally, it was found that exposure to HTPs caused an immediate increase in platelet-dependent blood clot formation propensity, as confirmed by the Total Thrombus-formation Analysis System (T-TAS). This discovery suggests that components present in HTP aerosol may lead to platelet activation and increased risk of thrombosis, which is a significant risk factor for cardiovascular diseases. These findings have important implications for public health, particularly in the context of the growing popularity of HTPs as an alternative to traditional cigarette smoking [16]. Researchers from Greece confirmed the negative impact of HTPs on the circulatory system, considering parameters such as HR, systolic and diastolic blood pressure, PWV, malondialdehyde (MDA) as a measure of oxidative stress, thromboxane B2 (TxB2) affecting platelet activation, and carbon monoxide (CO). Analysis showed that the use of both forms resulted in an increase in the aforementioned physiological parameters, with CC showing significantly higher levels. Based on these findings, researchers suggest that transitioning from traditional to alternative forms will bring health benefits to former smokers [17].

Another parameter affecting the circulatory system is HDL-C, known as high-density lipoprotein cholesterol. It is responsible for transporting cholesterol to the liver where it undergoes metabolism, consequently leading to a decreased risk of cardiovascular diseases [18].

Huan Hu et al. have described the relationship between the use of HTPs and CC smoking and HDL-C levels by utilizing

data collected by the Japan Epidemiology Collaboration on Occupational Health, including results from physical, subjective, and laboratory examinations. Full data were collected from 36,503 employees of several companies, who were then divided into two research groups [19]. The study revealed that exclusive HTP users had a mean difference of -1.1 mg/dL in HDL-C concentration, compared to never-smokers. Dual users showed a decrease in HDL-C levels of -3.7 mg/dL, which was slightly less than traditional cigarette smokers, who had a mean difference of -4.3 mg/dL in HDL-C concentration, compared to never-smokers. Furthermore, the study showed that for every additional 10 cigarettes/HTPs used per day, a further decrease in HDL-C levels was observed among exclusive HTP users, dual users, and exclusive cigarette smokers. The results of this analysis suggest that transitioning from traditional cigarettes to HTPs may result in an increase in high-density lipoprotein cholesterol (HDL-C) levels, and potentially reduce the risk of coronary artery disease. However, there is still a risk associated with the emission of aerosol containing nicotine and other harmful substances [20].

Respiratory system. For a while now, the negative impact of traditional cigarettes on the respiratory system has been known to lead to increased oxidative stress, potentially resulting in the development of diseases such as asthma, COPD (chronic obstructive pulmonary disease), and lung cancer [21, 22].

In the publication by Moazed et al., the effects of smoking HTP products were compared to traditional cigarettes (CC). The study was conducted on both smokers and on rats. The results of the rat studies showed that both HTPs and traditional cigarette smoking led to similar changes, such as smaller body weight gains, a higher percentage of inflammatory cells in bronchoalveolar lavage fluid (BAL), and histological disruptions in respiratory epithelium. However, these changes were significantly less pronounced with HTPs than with traditional cigarettes. Interestingly, exposure to HTPs in rats led to neutrophilia in blood and thymus atrophy more often compared to exposure to traditional cigarette smoke. In studies involving smokers, no significant differences were observed in white blood cell count, CRP, or FEV1/FVC among individuals who smoked CC, HTPs, or switched from CC to HTPs [23].

Research in 2020 by Athanasia Pataka et al. evaluated the impact of HTPs on respiratory function in 50 participants, half of whom were smokers and the other half non-smokers. The results showed a significant increase in carbon monoxide (CO) levels and indicators of airway resistance, together with a decrease in oxygen saturation (SaO2%), and a significant decrease in FEF (forced expiratory flow) 25% and PEF (peak expiratory flow) in both groups. The authors suggest that further studies are necessary to assess the long-term effects of using IQOS® devices in different population groups [24].

A publication from 2021 presented the results of over three years of observation of habitual smokers suffering from COPD who switched to HTP devices. Since the participants experienced similar sensations to those when smoking traditional cigarettes, HTPs proved to be an effective substitute for CC. Over half of the participants managed to completely switch the type of tobacco products they used, while dual smokers reduced CC consumption by up to 70%. The study group that switched to HTPs products experienced improvements in both objective parameters (reduction in COPD exacerbations by approximately 40%), and subjectively related their overall health status and physical activity. Additionally, improvements in CAT (COPD Assessment Test) scores and the 6MWD (6-minute walk distance) test were comparable with results observed in COPD patients participating in intensive rehabilitation [25].

An important health aspect is the impact of passive smoking of HTPs on children. In a study published in 2024, oxidative stress levels, endothelial function, and platelet function were assessed in children exposed to passive smoke from HTPs, traditional tobacco cigarettes (CC), and those not exposed to smoke. In both research groups, an increase in the aforementioned parameters was observed, directly translating into an increased risk of cardiovascular disease in the future. However, no significant differences were observed between these groups, clearly indicating the need to protect children from passive smoking, regardless of the form of tobacco product and its negative effects [26].

Periodontal disease. Periodontal diseases affects 7.8% of the population worldwide, and the negative impact of smoking on the development of these diseases has been known for a long time. As early as 1859, Bergeron described the correlation between smoking and the development of ulcerative gingivitis. Over the course of several decades, many scientists conducted numerous studies and attempted to refute or confirm this theory [27, 28, 29]. However, there is scant information describing the relationship between the use of HTPs and gum diseases. Takashi Yoshioka et al. collected data provided by the Japanese 'Society and New Tobacco' during four years. Among the 10,439 individuals who participated in the surveys were traditional cigarette smokers, HTP users, dual smokers, former smokers, and non-smokers. Participants were asked whether they were affected by gum diseases, and if so, whether they were undergoing treatment (Fig. 1).

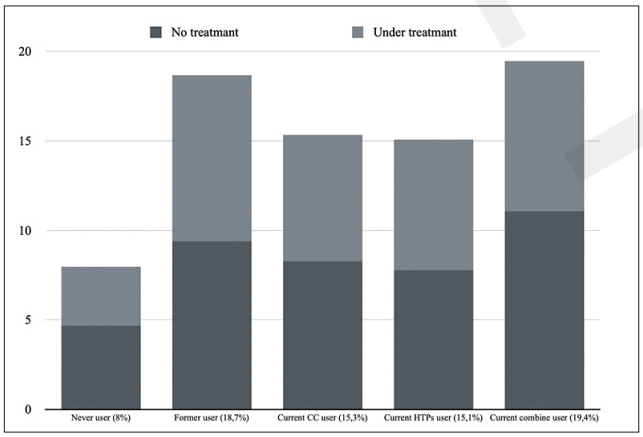

Figure 1. HTPs and CC effects on periodental disease

The results clearly show that gum diseases are most common among individuals who smoke both CC and HTPs (19.4%). The difference between users of tobacco heaters (15.1%) and traditional cigarette smokers (15.3%) is small, but in favour of HTPs (+0.2%). Among former smokers, the percentage of individuals struggling with gum diseases was also high at 18.7% [30].

The latest study from 2024 confirms that both CC smokers and IQOS® users have poorer gum health than non-smokers,

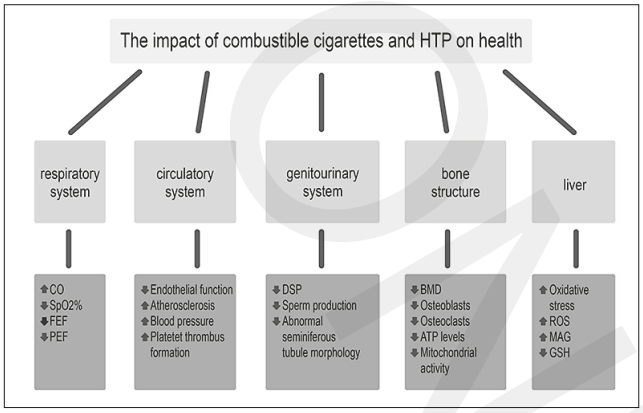

Figure 1.
FEF – forced expiratory flow; PEF – peak expiratory flow; DSP – Daily sperm production; BMD – bone mineral density; ROS – Reactive Oxygen Species; MAG-monoacylglycerol; GSH – Glutathione

as evidenced by increased indicators, such as probing pocket depth (PD), presence of gum bleeding, plaque accumulation, and clinical attachment loss (CAL). Although IQOS® users had better results compared to cigarette smokers, suggesting that IQOS® may be less harmful to gum health than traditional cigarettes, these devices still exhibit a negative impact on periodontal status [31].

Urogenital system. The influence of smoking on erectile function and the urogenital system is well-documented in scientific literature. A study conducted on a group of men in Australia showed that smoking is a significant risk factor for erectile dysfunction, with the risk increasing with the quantity of cigarettes consumed [32]. In studies of couples struggling with infertility, it has been observed that smokers have increased sperm pH, spermatogenesis disorders, reduced sperm count, sperm volume, and abnormalities in reproductive cell morphology, all of which negatively impact fertility [33].

Limited data is available regarding the impact of IQOS® devices on the aforementioned parameters. However, Seiichia Yoshida et al. in their study on mice, demonstrated that prenatal exposure of foetuses to aerosol from IQOS® devices leads to the aforementioned effects, and is associated with delayed sexual maturation. The study was conducted on 24 pregnant CD-1 mice exposed to aerosol from HTP devices, standard research cigarettes (3R4F), or were not exposed (control group). No differences were observed in parameters such as gestation length, litter size, offspring gender, body weight, testicular weight, or sex hormone levels. However, histological changes were observed in male offspring of mice exposed to IQOS® aerosol, examined after five weeks, such as seminiferous tubule damage through vacuolization and epithelial cell adhesion. Daily sperm production (DSP) was also reduced in male mice examined after five weeks, exposure to IQOS®, which was not observed in the 3R4F-exposed or control groups. However, DSP was similar among the three groups in mice examined after 15 weeks. This study demonstrates the negative impact of IQOS® on spermatogenesis and contributes to delaying sexual maturation to a greater extent than traditional tobacco products [34].

Liver. The impact of smoking IQOS® devices on liver function in rats has been investigated. Published data indicate that exposure to HTPs smoke leads to increased oxidative stress resulting in liver damage, manifested by increased production of reactive oxygen species, consequently leading to elevated levels of carbonylated proteins and malondialdehyde concentration in liver tissue. Additionally, researchers observed a significant decrease in glutathione, leading to a redox imbalance in the liver. The IQOS® device also affected changes in the lipid profile of the studied rats. Its use led to increased activation of the lipid oxidation pathway and an increase in parameters such as triglycerides, free sterols, monoacylglycerols, and oxycholesterols, which in the future may lead to liver damage and increase the risk of developing diseases such as fatty liver, cirrhosis, cancer, as well as cardiovascular diseases [35].

Bone structure. Osteoporosis is a disease characterized by excessive bone resorption, leading to increased susceptibility to pathological fractures. One of its primary risk factors is cigarette smoking. Numerous studies have indicated significant decreases in BMD (bone mineral density) among both former and current smokers [36, 37]. This phenomenon is partly due to the presence of various substances in tobacco smoke acting as ligands for the AhR receptor found in osteoclasts, which becomes activated and promotes the activation and excessive differentiation of osteoclasts responsible for bone resorption [38].

Weidong Weg et al. were among the first to investigate the impact of HTPs on the bone system. They conducted *in vitro* studies using SCP-1 cells (osteoprogenitor cells) and THP-1 cells (osteoclast precursor cells) exposed to the smoke from a reference cigarette and aerosol from HTP devices. The researchers examined the effects of both acute and chronic exposure. Cells exposed to 1R6F smoke on days three and seven of the study showed a decrease in the number of osteoblasts and osteoclasts, ATP levels, mitochondrial activity, total colony cell count, and an increase in LDH (lactate dehydrogenase). No such changes were observed in the other two groups. Only after 14 days and with a higher nicotine concentration in the aerosol, changes were observed in the colony exposed to HTP aerosol—there was a slight increase in LDH levels and a decrease in the total cell count. In the case of chronic exposure, increased osteoclast activity and decreased osteoblasts were observed, favouring bone resorption. The activity of osteoclasts in the colony exposed to HTP aerosol was at a similar level to that of the control group.

The study demonstrated that aerosol from HTPs has a lesser negative impact than tobacco smoke from conventional cigarettes and provides a viable alternative for individuals grappling with addiction [39].

CONCLUSIONS

The studies cited above show that the use of HTPs leads to increased oxidative stress, activation of the sympathetic nervous system, and dysfunction of the endothelium. These changes can result, among other things, in a transient increase in arterial stiffness, a tendency to form blood clots, and a decrease in high-density lipoprotein (HDL-C) levels, negatively impacting the risk of cardiovascular diseases. Regarding the respiratory system, it has been demonstrated that HTPs use can lead to similar pathological changes as traditional cigarette smoking, albeit to a lesser extent, and

may improve respiratory parameters and quality of life in individuals suffering from COPD. The impact of HTPs on the genitourinary system has not yet been fully explored, but there are studies suggesting a negative effect on erectile function and reproductive functions in men, leading to changes such as disturbances in spermatogenesis or a decrease in sperm volume. Regarding periodontal diseases, a slight difference in the number of affected individuals compared to those using CC was observed; however, it still favoured HTPs.

The aforementioned studies also show that HTPs devices have a lesser impact on pathological activation of osteoclasts and bone resorption than traditional cigarettes. However, there is still a risk associated with their use. It has also been demonstrated that HTPs have a lesser impact on acute liver damage and other liver diseases, such as cirrhosis.

In summary, the research indicates that HTPs devices may reduce the risk of health damage compared to CC by reducing toxic and carcinogenic substances in the aerosol emitted by these devices. Despite promising results, concerns remain about the impact of these devices on the human body, and further research in this direction is necessary.

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