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The health effects of electronic cigarette use: An overview

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Abstract

E-cigarettes were first introduced as smoking cessation aids and then expanded among non-smokers. E-cigarettes are relatively new and their impact on health has not been sufficiently explored, particularly in the long-term. The aim of this study was to review the effect of e-cigarettes on general and oral health. E-cigarette use is considered significantly less harmful than smoking though it is not deprived of health risks, which might vary depending on e-liquid and e-vapor content, manufacturing and storage conditions and prolonged use. Flavorings, propylene glycol, glycerin, aldehydes, heavy metal traces and nicotine are some of their hazardous compounds. E-cigarettes affect several cellular activities, such as inflammatory and apoptotic response, cellular metabolism and proliferation, commensal microbe proliferation and virulence. They have cytotoxic, genotoxic, and carcinogenic properties. Chronic use affects mostly the respiratory and cardiovascular systems and possibly the central nervous system. They increase heart rate, blood pressure, arterial stiffness and risks of presenting heart diseases that pave the way for cardiac arrhythmias. Periodontal tissues presented less inflammation with e-cigarettes than smoking. Periimplant tissues presented higher proinflammatory cytokine levels with e-cigarettes than never-smoking. Oral mucosal lesions were in total similarly prevalent for e-cigarette users and former smokers, though nicotine stomatitis, hairy tongue and angular cheilitis were more frequent with e-cigarettes. C. albicans carriage was higher with e-cigarettes than never-smoking. Switching from smoking to e-cigarettes may reduce oral and throat symptomatology, though several oral health consequences might be associated with e-cigarettes. Evidence supports that chronic e-cigarette use may affect health negatively. Taking into consideration that e-cigarettes might help quit smoking, health professionals should inform patients that smokers selecting e-cigarettes as smoking cessation aid should soon discontinue them since prolonged use entails health risks. Moreover, health professionals should inform non-smokers that e-cigarettes are not harmless and discourage them from starting vaping.

Introduction

Smoking has deleterious consequences on the general health and the oral cavity. The consequences on health causally linked to smoking include cancers and chronic diseases. For smokers, the inhalation of chemical compounds originating from tobacco burning is a severe health threat. The chronic nicotine consumption leads to nicotine addiction. Furthermore, secondhand and thirdhand smoking entail risks [1]. Therefore, health professionals should inform patients on the detrimental effect of smoking and the beneficial effect of smoking cessation on health, as well as advise, motivate and support their patients to quit smoking. The health professionals' role in the smoking cessation effort is of outmost importance [2].

Several pharmacological and behavioural strategies and their combination are used in the smoking cessation effort [2]. Electronic cigarettes (e-cigarettes or e-cigs or ECs) were first introduced in the market as smoking cessation aids. However, their use quickly expanded among non-smokers as well [3]. E-cigarettes are electronic nicotine delivery systems (ENDS), where tobacco is not necessary for their operation [4]. With e-cigarettes with refillable tanks, the heating element vaporizes a small amount of a liquid (e-cigarette liquid or e-liquid) in every "puff" and the user inhales an aerosol/vapor (e-cigarette vapor or e-vapor), instead of smoke [5,6].

Most e-liquids contain *nicotine, glycerol, propylene glycol, ethylene glycol, 1,3-propanediol, 1,2-propanodiol, thujone, ethyl vanillin* [7-10] and flavorings [9], with *propylene glycol* and *glycerin* being their main ingredients. The main flavorings of the e-liquids are aldehydes (*formaldehyde, acetaldehyde, acrolein, crotonaldehyde, benzaldehyde*) [9], nitrosamines (*nitrosonornicotine, 4-(nitrosomethyl-amino)-1-(3-pyridyl)-butanone and nitrosoanatabins*) [11], *acetone* [12], *terpenic molecules* [9], *vanillin and ethyl vanillin, maltol and ethyl maltol, benzyl alcohol, ethyl butyrate and ethyl acetate* [13]. E-liquid market unveils new flavors with flavoring components that have not been tested yet. The e-liquid might or might not contain nicotine depending on the user's choice [11]. In case the e-liquid contains nicotine, the nicotine concentration is selected by the user [11]. Most e-liquid nicotine concentrations do not exceed the 87.2 mg/ml [14].

E-cigarette use is considered significantly less harmful than conventional smoking [15]. Nonetheless, the diversity in the e-liquid and e-vapor content might affect the possible health risks. Furthermore, the absence of standardized manufacturing protocol for e-liquids does not exclude contamination with cancer-inducing substances [16-19], while the absence of strict regulation for the storage of e-cigarettes allows storage under various conditions. When stored in open containers, the oxidation of nicotine is possible which leads to the unintentional presence of degradation products [20]. Moreover, heavy metals have been detected in e-cigarettes' vapor (or aerosol), mainly nickel and chromium, which probably derive from the cartridge [21,22]. It is therefore clear that the health risks of the e-cigarettes have not been sufficiently explored. The aim of the present study was to

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thoroughly review the possible effect of the e-cigarettes on the general and oral health.

Effects on general health

Heat generation

The heat generated by e-cigarettes is significantly lower (up to 160 °C, depending on the model) [23] than that generated by smoking a conventional tobacco cigarette (approximately 1.000 °C per puff) [24]. Combustion related toxic chemicals are generated by cigarette smoking [24], whereas they are not emitted with e-cigarettes [23].

Chemical compounds

Several chemical compounds of the e-liquids and e-vapors might be harmful. Certain compounds of the e-vapor have cytotoxic, genotoxic, and carcinogenic properties [25]. Generally, most studied e-liquids are much less cytotoxic than cigarette smoke extract [26-28].

E-vapor, regardless of nicotine and flavoring content, suppresses cellular antioxidant defenses [29] and induces carbonyl/oxidative stress [30], oxidative DNA damage [29,30], mainly attributed to aldehydes [31,32], inflammation and endothelial barrier dysfunction [33] leading to reduced cell viability and clonogenic survival, along with increased rates of apoptosis and necrosis [30] with the end result of tissue damage [34-37]. Even short-term exposure to e-vapor may cause oxidative DNA damage [29,30]. Moreover, the radical oxygen species increase [38] and the expression of proteins implicated in oxidative DNA damage repair decrease, which might raise the cancer risk [34]. However, e-vapor is less harmful for cell viability as compared to e-liquid [39-41]. Factors related to the chemical content, the particle size and the particle number concentration of the e-vapor seem to affect its toxicity [42].

Glycol/ Glycerin

At two hours after e-cigarette use, *nicotine, 1,2-propanediol, aluminum, glycerin and polycyclic aromatic* hydrocarbons increase in blood to levels that they might be carcinogenic [43]. Though, *1,2-propanediol* and *ethylene glycol* entail significantly less health risks as compared to nicotine [44]. In terms of *propylene glycol*, exposure to it irritates the eyes and lungs [45], whereas repeated inhalation affects the central nervous system and the spleen [46].

Heavy metals

Repeated inhalation of nickel and chromium originating from the e-vapor is toxic and might lead to the formation of carcinogens, which then line the pulmonary alveoli [47].

Flavoring components

The flavoring components are mostly responsible for the cytotoxic effects of the e-liquids [48]. Certain flavors are more cytotoxic than others with cinnamon flavor being the most toxic [27,38, 39,49]. Particularly, it negatively affects the respiratory epithelial cells innate immunity mechanisms and the neutrophil phagocytosis [50-52] and it seems to be genotoxic for embryonic cells [53,54]. These effects were attributed to the impairment of cellular bioenergetics [50-52]. Furthermore, e-liquid flavors containing aromatic aldehydes and their derivatives caused neutrophil distraction [52]. Menthol flavored e-cigarettes generate larger particles and less nanoparticles as compared to tobacco flavored e-cigarettes, whereas nicotine increases the nanoparticle levels [42]. Exposure of cell lines to menthol flavored e-liquids significantly reduced cell proliferation and viability, which might indicate that menthol additives should be avoided [55]. Flavor compounds thujone and ethyl vanillin appear to be rather safe [44]. Exposure of osteoblasts to e-liquids decreased cell viability, which was flavor-dependent irrespective of nicotine presence [56]. Moreover, flavored e-liquids revealed collagen type I as a potential target in osteoblasts [56]. Nevertheless, it should be taken into consideration that most e-liquid flavors have been tested for their safety during heating and digestion, but not during inhalation [57].

Nicotine

With cigarette smoking, nicotine reaches peak blood concentrations within a few minutes [58,59]. The peak nicotine blood concentrations are higher with cigarette smoking than e-cigarettes [60-62]. Cotinine levels (the predominant metabolite of nicotine) are significantly higher for cigarette smokers than dual users (individuals using both tobacco cigarettes and e-cigarettes) [63]. Though, overall nicotine exposure levels were reported to be similar for cigarette smokers and chronic e-cigarette users [64, 27]. Larger ENDS, such as tank/modified, can produce blood nicotine concentrations approaching those of cigarettes, but with a slower absorption rate [65]. Higher blood nicotine levels are more common among experienced e-cigarette users [27].

Based on the Centers for Disease Control and Prevention report [66]. "E-cigarettes and other products containing nicotine are not safe to use during pregnancy. Nicotine is a health danger for pregnant women and developing babies and can damage a developing baby's brain and lungs. Also, some of the flavorings used in e-cigarettes may be harmful to a developing baby." In terms of pregnancy, a safe concentration of nicotine use has not been reported and nicotine exposure to utero is associated with adverse effects to respiratory, cardiovascular and central nervous system of the fetus [67].

A recently published systematic review revealed that nicotine at concentrations found in the plasma, the saliva and the gingival crevicular fluid of tobacco smokers, nicotine replacement therapy users and e-cigarette users is unlikely to be cytotoxic to human gingival and periodontal ligament cells in vitro [68]. Inhibition of cell attachment was observed with exposure to nanomolar (nM) concentrations of nicotine, while cell proliferation was inhibited by higher nicotine concentrations [68]. Antiproliferative impact of nicotine on leukocytes, as well as inhibition of neovascularization and osteoblastic differentiation were found in vitro [69-71].

Systems affected by e-cigarette use

Chronic e-cigarette use affects mostly the respiratory and cardiovascular systems, whereas there are indications that it may affect the central nervous system as well (Table 1) [63-98].

Respiratory system

E-cigarette use has adverse effects on the respiratory system. Local (mouth/throat) irritation of the tissues, allergic reactions [63], shortness of breath, coughing, wheezing [21] and pneumonia [4] have been reported in e-cigarette users. Most cases are mild and resolve, though certain cases might become serious [27]. Short-term use of ENDS causes an increase in impedance, peripheral airway flow resistance, and oxidative stress among healthy users [72,73], while exposure to propylene glycol can cause upper and lower respiratory tract irritation [45,74]. E-vapor droplets are larger during the inhalation as compared to the exhalation phase, which indicates increased levels of nicotine delivery during vaporization [75]. This inhaled nicotine can lead to airway remodeling, profibrogenic and dysregulated repair [35]. ENDS inhalation has been found to induce toxicity, oxidative

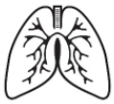
	Health effects	E- vapor/E- liquid component
	Eyes irritation	Propylene Glycol
	Lungs irritation/Inflammation	Propylene Glycol, Aldehydes, Heavy Metals
	Pulmonary cancer	Flavorants, Heavy Metals
	Nasopharyngeal cancer	Carbonyl Compounds
	CNS/behavior defects	Propylene Glycol, Heavy Metals
	Positive cognitive effects	Nicotine
	Spleen damage	Propylene Glycol
	Increased oxidative stress and DNA damage (increased cancer risk)	Flavorants
	Neutrophil phagocytosis impairment	Flavorants
	Inhibition of leukocyte proliferation	Nicotine
	Increased glycated hemoglobin, inhibition of neovascularization, NO increase, cardiovascular toxicity	Nicotine
	Heart rate and blood pressure increase, arterial stiffness and the heart diseases risk	Glycerol
	Impairment of osteoblastic differentiation	Nicotine
	Osseotoxicity	Flavorants

Table 1. Health risks related to e-cigarette use by e-vapor/e-liquid compound [63-98]

stress, and inflammatory response in the epithelial cells of the lungs [35,36,76], consequently increasing allergen-induced airway hyper-responsiveness [77], altering innate immunity/host response, and enhancing virulence of colonizing bacteria [76,78,79] and virus infection [78], hence affecting local microbiome [80]. Asthma [21] and bronchiolitis obliterans (popcorn lung) seem to be associated with e-cigarette use [80]. Nasopharyngeal cancer was reported in chronic e-cigarette users, where carbonyl compounds were mainly implicated, such as formaldehyde and heavy metals [81-83].

Aldehydes, such as benzaldehyde and vanillin, induce respiratory irritation [84], while other flavoring chemicals including ortho-vanillin (vanilla), maltol (malt), cinnamaldehyde, and coumarin induce pro-inflammatory response in lung cells in vitro [85]. Specifically, individuals with a history of asthma might be sensitive to propylene glycol [86]. In individuals with chronic respiratory disease, neutrophil disarrangement due to flavors seems to decrease bacterial clearance. Consequently, aldehyde flavored e-liquids may increase the risk of infections or respiratory diseases [52,87].

When the contribution of nicotine in cigarette smoking or e-cigarettes to lung endothelial injury was evaluated, it was found that nicotine induced dose-dependent loss of endothelial barrier in cultured cell monolayers and rapidly increased lung inflammation and oxidative stress in mice. Nicotine-independent effects of e-cigarette liquids were found, which might be attributed to acrolein, detected along with propylene glycol, glycerol, and nicotine in both e-cigarette liquids and vapors. It was suggested that soluble components of e-cigarettes, including nicotine, cause dose-dependent loss of lung endothelial barrier function, which is associated with oxidative stress and increase of inflammation [33].

In terms of heavy metals, exposure to nickel leads to chronic inflammatory response in the lungs, which causes alveolar epithelium hyperplasia, fibrosis, bronchiolization, alveolar proteinosis and artily of the nasal olfactory epithelium [88,89]. Chromium has also a damaging impact on the respiratory system by causing ulceration, chronic rhinitis and pharyngitis, impaired lung function and emphysema [21].

Cardiovascular system

When vaping, 20 to 27% of the e-cigarette exclusive supersaturated *propylene glycol* (aka *1,2-propanediol*) and vegetable glycerin-based liquid particles are inhaled through the lungs and become deposited into the circulatory system [90]. E-cigarettes were found to increase the heart rate, the blood pressure, the arterial stiffness and the risk of getting heart diseases that pave the way for cardiac arrhythmias [91,92]. These cardiovascular diseases are mainly attributed to glycerol contained in e-cigarettes, since it can turn into an irritant substance when heated [93]. Moreover, aerosolized nicotine may increase the release of the inflammatory signaling molecule nitric oxide (NO) and induce cardiovascular toxicity upon inhalation [43]. Congestive heart failure and hypotension have been reported in relation to e-cigarettes [4].

Central nervous system

There are indications that e-cigarettes have positive cognitive effects consistent with the acute positive benefits of nicotine, such as improved memory and mood, and positive cognitive effects in abstinent smokers [27]. However, disorientation and epileptic seizures following e-cigarette use have been reported [4]. Heavy metal traces, such as nickel, chromium and lead, seem to affect neural function. Exposure to Ni and Cr may induce lethargy and ataxia [88], while lead

was found to cause changes in nerve velocity and encephalopathy [94-96]. In children, exposure to lead, even in low concentrations, might induce neurocognitive toxicity [97,98], which might lead to paralysis, convulsions, delirium or even coma [21].

E-cigarette use and oral health

Despite the rising concern of the effects of e-cigarette use on the general health, the evidence on their possible effect on the oral health remains limited [99-101].

In vitro/ in vivo studies

E-cigarettes affect several cellular activities, such as inflammatory and apoptotic response, cellular metabolism and proliferation, commensal microbe proliferation and virulence.

Inflammatory and apoptotic response: Exposure to e-vapor, regardless of nicotine presence, may increase oxidative/ carbonyl stress and inflammatory cytokine release in human periodontal ligament fibroblasts (HPdLF), human gingival epithelium progenitors pooled cells (HGEPp), human gingival fibroblasts (HGF) and normal human oral keratinocytes (NHOK), with greater response by flavored e-liquids [42,101,102]. This alteration has been attributed to protein carbonylation and to a significant decrease of intracellular glutathione (GSH) [42,101]. Particularly, reactive aldehydes/carbonyls derived from e-vapor can cause protein carbonylation and DNA adducts, leading to inflammation and DNA damage [101]. DNA damage in cell lines and in 3D models of EpiGingival tissues has been associated with cell apoptosis via caspase-3 pathway [100], while injurious oxidative stress may lead to significant cytotoxicity [42,102]. Moreover, protein carbonylation results in autoantibody production, which may lead to destruction of periodontal tissues [34,37]. Hence, it is possible that carbonyls/aldehydes play an important role in the e-vapor-induced oral toxicity [80]. Furthermore, increased carbonyl/oxidative stress results in premature cellular senescence (a state of irreversible growth arrest which amplifies chronic inflammation) due to persistent DNA dam age via RAGE-HDAC2-depedent pathways in gingival epithelium [80, 101].

Cellular metabolism and proliferation: Regardless of the presence of nicotine in e-cigarettes, the metabolic activity of human gingival fibroblasts (HGFs) seems to decrease, when exposed to e-liquids. Pre-warming through the cartomizer increased this reduction [102]. The cell migration of human periodontal ligament fibroblasts was statistically significantly reduced for fibroblasts exposed to menthol flavored liquids as compared to non-exposed fibroblasts and to nicotine treated fibroblasts [55].

Commensal microbe proliferation and virulence: Flavorless e-vapor did not significantly affect the survival and growth of oral commensal streptococci [103]. Though, e-liquids of high viscosity and e-liquids with sweet flavoring components provide attachment and additional nutrition for cariogenic bacteria, such as S. mutans [104]. This implies that e-cigarettes might be harmful for dental tissues [104]. Moreover, nicotine-rich e-vapors were found to increase C. albicans proliferation and promote its interaction with gingival epithelial cells [105]. Therefore, it seems that e-cigarettes may increase the risk of oral candidiasis.

Clinical studies

Clinical studies on e-cigarette use are very limited and present inherent difficulties and limitations. E-cigarette use has been studied in relation to the periodontal and peri-implant condition and the oral mucosal lesions.

Comparisons among conventional cigarette smokers, e-cigarette users and never-smokers found worse inflammation of the periodontal tissues [106,107] and higher levels of proinflammatory cytokines in the gingival crevicular fluid [107] for conventional cigarette smokers as compared to the other groups. Higher levels of proinflammatory cytokines were detected in the peri-implant sulcus fluid for cigarette smokers and e-cigarette users as compared to never-smokers, which was partly attributed to nicotine [108].

A prospective case-control study found that the total prevalence of oral mucosal lesions was similar for e-cigarette users and former cigarette smokers, though nicotine stomatitis, hairy tongue and angular cheilitis were more frequent for e-cigarette users [109]. The higher prevalence of nicotine stomatitis for e-cigarette users as compared to former cigarette smokers was partly attributed to nicotine and partly to the chemical components of e-cigarettes [109], such as the flavoring components with strawberry-flavor being the most toxic [110]. Moreover, C. albicans carriage was significantly higher for e-cigarette users than never-smokers, but it did not significantly differ between e-cigarette users and conventional cigarette smokers [111]. The higher C. albicans carriage for e-cigarette users than never-smokers was attributed to the positive effect of nicotine on growth and proliferation of oral yeasts [112] and to the nicotine-induced changes, namely increased epithelial keratinized tissues thickness, suppressed polymorphonuclear leukocytes function and reduced secretory immunoglobulin A salivary levels [113-115].

A recent systematic review [25] aiming to evaluate the possible impact of e-cigarette use on the oral health found that most of the oral and throat symptoms experienced by the e-cigarette users were relatively minor and transient. There was evidence that conventional cigarette smokers who switched to e-cigarettes experienced alleviation of these symptoms. E-cigarette use increased the risk of deteriorating periodontal and dental health as well as changes to the oral microbiome. The authors of this systematic review concluded that although switching from conventional cigarette smoking to e-cigarettes may reduce oral symptomatology, the findings suggest that a wide range of oral health sequelae may be associated with e-cigarette use [25].

In a recent study, deregulation of very important genes and disruption of associated molecular pathways, mostly related to carcinogenesis, were detected in oral epithelial cells of e-cigarette users. Interestingly, most of the deregulated transcripts were different between conventional smokers and e-cigarette users [116].

E-cigarettes as a smoking-cessation product

A recent randomized clinical trial [117] evaluated the effectiveness of e-cigarettes in the attempt to stop smoking as compared to that of nicotine products approved as smoking-cessation treatments, specifically nicotine-replacement products. The control group individuals were assigned to nicotine-replacement products of their choice, including product combinations, provided for up to 3 months, and the test group individuals were assigned to e-cigarettes, with e-liquid refills of their choice. Both treatment groups received weekly behavioral support for at least 4 weeks. The primary outcome was sustained abstinence for 1 year, which was validated biochemically at the final evaluation. The secondary outcomes were participant-reported treatment usage and respiratory symptoms. The 1-year abstinence rate from smoking was statistically significantly higher for the e-cigarette (18.0%) than the

nicotine-replacement group (9.9%). Among individuals with 1-year abstinence from smoking, the e-cigarette group individuals were more likely (80%) than those in the nicotine-replacement group (9%) to use their assigned product at 52 weeks. Throat or mouth irritation was reported more frequently for the e-cigarette (65.3%) than the nicotine-replacement (51.2%) group and nausea less frequently for the e-cigarette (31.3%) than the nicotine-replacement (37.9%) group. The e-cigarette group reported greater declines in the incidence of cough and phlegm production from baseline to 52 weeks than did the nicotine-replacement group. The incidence of wheezing or shortness of breath was similar for both treatment groups. The authors of this study concluded that e-cigarettes were more effective for smoking cessation than nicotine-replacement therapy, when both products were accompanied by behavioral support [117].

A cross-sectional study conducted in a group of American adults who visited their physician, dentist or child's doctor during the past 12 months revealed that only a few physicians and dentists provided information and advice on the possible harmful and beneficial effects of e-cigarettes and dentists provided the lowest rates of advice [118]. Moreover, despite the significant differences in knowledge and perception of e-cigarette use between dental students from two dental schools, one of the United States and one of Spain, both populations reported to be uncomfortable discussing about e-cigarette safety and long-term effects on oral cavity with [119]. Most students were willing to receive more information on e-cigarettes and the integration of a relative program into the dental curriculum [119]. Taking into consideration these results together with the steadily raising e-cigarette use, it seems that it is important to increase awareness and create evidence-based guidelines for the health professionals in order to help the patients in the attempt to quit smoking.

The following guidelines on e-cigarette use were provided in an editorial published on behalf of the American Heart Association.

- The most effective treatment for smoking cessation is behavioral counseling combined with products approved by the Food and Drug Administration (FDA) as smoking-cessation products. Although e-cigarettes have not been approved as a smoking-cessation product by the FDA, smokers who are unable to stop smoking with approved FDA products may benefit from the use of e-cigarettes as a cessation aid, despite the limited evidence. E-cigarettes are likely to help reduce urges to smoke and ease withdrawal from cigarettes, since they delivery nicotine. E-cigarettes are not free of health risks, but evidence suggests that they expose the users to much lower levels of toxins as compared to the use of combustible tobacco cigarettes. Mouth/ throat irritation and dry cough are the most common side effects of e-cigarettes. The long-term risks of e-cigarettes are unknown. Upon successful cessation of combustible tobacco cigarettes, e-cigarette use should be discontinued.
- E-cigarettes are available in different models, which differ in the way they are used, the nicotine delivery levels and the flavors. More advanced E-cigarette models that deliver nicotine more efficiently seem to work best for those trying to quit smoking. The e-cigarette user should use and care each device according to the manufacturer's recommendations. The e-cigarette user and/ or prospective users should retrieve information on e-cigarettes from the FDA's website (https: //www.fda.gov/TobaccoProducts/ Labeling/ProductsIngredientsComponents/ucm456610.htm). E-cigarette use on a daily basis is generally more successful for quitting smoking than on an intermittent basis. Learning to use the device to deliver the proper amount of nicotine to relieve the urge to smoke might require practice. For the individual attempting to quit smoking by using e-cigarettes, it is recommended to quit conventional cigarette smoking the soonest possible and then discontinue e-cigarette use as soon as he/she feels that he/she managed to quit cigarette smoking. Dual use of conventional tobacco cigarettes and e-cigarettes should be avoided whenever possible. The use of e-cigarettes might be combined with the use of FDA approved smoking-cessation products.
- Ingestion of nicotine liquids can be dangerous. E-liquids should be kept in childproof containers and out of the reach of children. E-cigarette devices should be protected from extreme temperatures. Moreover, battery explosions should be prevented by: (a) using devices with safety features such as button locks, vent holes, and protection against overcharging; (b) keeping batteries in a case to prevent contact with metal objects; (c) not charging the device with a phone or tablet charger; (d) not charging the device unattended; and (e) replacing batteries if they get damaged or wet.
- E-cigarette use indoors is not allowed in many public places. With e-cigarettes, the risk from secondhand use is lower than that from smoking, outdoor use is preferable and by keeping safe distances from other individuals.

It is worthwhile to notice than nowadays e-cigarettes are used by non-cigarette smokers as well [3]. E-cigarettes are popular among youth and adolescents, which raises concerns as they may present a possible gateway to future smoking [45, 120-123] or that their use may preserve nicotine addiction [124].

Impact on the environment

The possible impact of e-cigarette use on the environment cannot be excluded. It is important to take into consideration that e-cigarettes are not emission-free and that vapor contains potential harmful chemicals, hence health risks to non-smokers are possible [125]. However, the emissions from conventional cigarettes are more toxic than those from e-cigarettes [27,126]. Moreover, environmental tobacco smoke derives mostly from the emission between puffs, but this emission is totally avoided with e-cigarette use [75] and therefore e-vapor contains only exhaled substances [125]. Smoking delivers 1,500 times more harmful and potentially harmful constituents compared to e-vapor in the air [127], but if all the emissions from e-cigarettes were exhaled, 25 times more exhaled particle matter would still be created than what exists in a typical urban environment [126]. Interestingly, nicotine-enriched e-cigarettes produced lower particle matter levels than nicotine-free e-cigarettes [128]. Increased particulated matter may lead to respiratory and cardiovascular diseases [125]. Furthermore, even though nicotine deposits and particulate matter [62] were lower in e-cigarette use than smoking, they can still accumulate on indoor surfaces and can be absorbed transdermally [27, 129-133]. Nevertheless, certain trace metals are in higher concentration in the e-vapor as compared to the cigarette smoke, such as nickel, silver and chromium [22,134]. These compounds have been associated with organ toxicity, neurological defects and cancer [21,125].

Concerning children's exposure to secondhand vapor, nicotine exposure to brain and lungs during periods of development (fetus, childhood and adolescence) should be taken into consideration as a subject of concern because of the susceptibility of these organs [135]. Except for the health risks posed by secondhand smoke and secondhand vapor, it was found that this exposure increases young

people's susceptibility to future tobacco use, and thus health risk is even more increased [136].

Conclusion

In conclusion, although the data on short-and long-term effects of e-cigarettes are inconclusive, the accumulating evidence supports that chronic e-cigarette use may affect health negatively. E-cigarettes seem to be implicated in defects of several systems, tissues and organs, such as respiratory, cardiovascular, neurological and oral. However, further long-term and large-scaled studies are required to investigate the risks of e-cigarette use on human health. Taking into consideration that e-cigarette use might help in the attempt to quit conventional cigarette smoking, health professionals should inform their patients that cigarette smokers selecting e-cigarettes as a smoking cessation aid should discontinue the e-cigarette use as soon as they feel that they managed to quit cigarette smoking since their prolonged use might entail health risks. Moreover, health professionals should inform their non-smoker patients that e-cigarettes are not harmless and discourage them from starting vaping since this might lead to chronic e-cigarette use or become the gateway for future cigarette smoking, especially for younger individuals.

Authorship and contribution

All authors contributed equally to study design, data collection and paper preparation.

Competing interest

The authors declare that they have no competing interests and that no funding was used for this study.

References

1. Tsantila S, Alexandridi F, Pepelassi E (2017) Smoking and periodontal treatment outcome. *J Dent Pathol Med* 1: 103-110.
2. Alexandridi F, Tsantila S, Pepelassi E (2018) Smoking cessation and response to periodontal treatment. *Aust Dent J* 63: 140-149
3. Vakaki C, Gkoulitou E, Pepelassi E (2019) Electronic Cigarettes: An overview of types, content, use and legislation. *J Dent and Dental Med* 2: 1-9.
4. Pisinger C, Døssing M (2014) A systematic review of health effects of electronic cigarettes. *Prev Med* 69: 248-260.
5. Jorenby DE, Smith SS, Fiore MC, Baker TB (2017) Nicotine levels, withdrawal symptoms, and smoking reduction success in real world use: A comparison of cigarette smokers and dual users of both cigarettes and E-cigarettes. *Drug Alcohol Depend* 170: 93-101.
6. Ruhe M, Haller-Stevenson E, Roulston K, Jourdan M (2017) Strengthening the capacity of local health departments to reduce exposure to electronic nicotine delivery systems. *J Public Health Manag Pract* 23: 93-94.
7. Polosa R, Rodu B, Caponnetto P, Maglia M, Raciti C (2013) A fresh look at tobacco harm reduction: the case for the electronic cigarette. *Harm Reduct J* 10: 19.
8. McAuley TR, Hopke PK, Zhao J, Babaian S (2012) Comparison of the effects of e-cigarette vapor and cigarette smoke on indoor air quality. *Inhal Toxicol* 24: 850-857.
9. Varlet V, Farsalinos K, Augsburger M, Thomas A, Etter JF (2015) Toxicity assessment of refill liquids for electronic cigarettes. *Int J Environ Res Public Health* 12: 4796-4815.
10. https: //www.fda.gov/media/71029/download
11. Nayir E, Karacabey B, Kirca O, Ozdogan M (2016) Electronic cigarette (e-cigarette). *J Oncol Sci* 2: 16-20.
12. https://ec.europa.eu/food/sites/food/files/safety/docs/sci-com_scf_reports_29.pdf
13. https://www.uspnf.com/sites/default/files/usp_pdf/EN/USPNF/generalChapter467IRA.pdf
14. National Academies of Sciences, Engineering, and Medicine (2018) Public health consequences of e-cigarettes. Washington (DC): National Academies Press.
15. McNeill A, Brose LS, Calder R, Hitchman SC, Hajek P et al. (2015) E-cigarettes: an evidence update. A report commissioned by Public Health England. *Public Health England* 111.
16. Chen IL (2013) FDA summary of adverse events on electronic cigarettes. *Nicotine Tob Res* 15: 615-616.
17. Etter JF, Zäther E, Svenss on S (2013) Analysis of refill liquids for electronic cigarettes. *Addiction* 108: 1671-1679.
18. Goniewicz ML, Kuma T, Gawron M, Knysak J, Kosmider L (2013) Nicotine levels in electronic cigarettes. *Nicotine Tob Res* 15: 158-166.
19. Kim HJ, Shin HS (2013) Determination of tobacco-specific nitrosamines in replacement liquids of electronic cigarettes by liquid chromatography- tandem mass spectrometry. *J Chromatogr A* 1291: 48-55.
20. Martinez RE, Dhawan S, Sumner W, Williams BJ (2015) On-Line Chemical Composition Analysis of Refillable Electronic Cigarette Aerosol- Measurement of Nicotine and Nicotyrine. *Nicotine Tob Res* 17: 1263-1269.
21. Gaur S, Agnihotri R (2019) Health effects of trace metals in electronic cigarette aerosols—a systematic review. *Biol Trace Elem Res* 188: 295-315.
22. Williams M, Villarreal A, Bozhilov K, Lin S, Talbot P (2013) Metal and silicate particles including nanoparticles are present in electronic cigarette cartomizer fluid and aerosol. *PLoS ONE* 8: e57987.
23. http: //www.healthnz.co.nz/DublinEcigBenchtopHandout.pdf.
24. Baker RR (2006) Smoke generation inside a burning cigarette: Modifying combustion to develop cigarettes that may be less hazardous to health. *Prog Energy Combust* Sci 32: 373-385.
25. Yang I, Sandeep S, Rodriguez J (2020) The oral health impact of electronic cigarette use: a systematic review. *Crit Rev Toxicol* 1-30.
26. Cervellati F, Muresan XM, Sticozzi C, Gambari R, Montagner G et al. (2014) Comparative effects between electronic and cigarette smoke in human keratinocytes and epithelial lung cells. *Toxicol In Vitro* 28: 999-1005.
27. Glasser AM, Collins L, Pearson JL, Abudayyeh H, Niaura RS et al. (2017) Overview of electronic nicotine delivery systems: a systematic review. *Am J Prev Med* 52: 33-66.
28. Misra M, Leverette RD, Cooper BT, Bennett MB, Brown SE (2014) Comparative in vitro toxicity profile of electronic and tobacco cigarettes, smokeless tobacco and nicotine replacement therapy products: e-liquids, extracts and collected aerosols. *Int J Environ Res Public Health* 11: 11325-11347.
29. Ganapathy V, Manyanga J, Brame L, McGuire D, Sadhasivam B et al. (2017) Electronic cigarette aerosols suppress cellular antioxidant defenses and induce significant oxidative DNA damage. *PloS ONE* 12: e0177780.
30. Yu V, Rahimy M, Korrapati A, Xuan Y, Zou AE et al. (2016) Electronic cigarettes induce DNA strand breaks and cell death independently of nicotine in cell lines. *Oral Oncol* 52: 58-65.
31. Cheng T (2014) Chemical evaluation of electronic cigarettes. *Tob Control* 23: 11-17.
32. Kosmider L, Sobczak A, Fik M, Knysak J, Zaciera M et al. (2014) Carbonyl compounds in electronic cigarette vapors: Effects of nicotine solvent and battery output voltage. *Nicotine Tob Res* 16: 1319-1326.
33. Schweitzer KS, Chen SX, Law S, Demark MV, Poirier C et al. (2015) Endothelial disruptive proinflammatory effects of nicotine and e-vapor exposures. *Am J Physiol Lung Cell Mol Physiol* 309: 175-187.
34. Baltacioglu E, Akalin FA, Alver A, Deger O, Karabulut E (2008) Protein carbonyl levels in serum and gingival crevicular fluid in patients with chronic periodontitis. *Arch Oral Biol* 53: 716-722.
35. Lei W, Lerner C, Sundar IK, Rahman I (2017) Myofibroblast differentiation and its functional properties are inhibited by nicotine and e-cigarette via mitochondrial OXPHOS complex III. *Sci Rep* 7: 43213.
36. Lerner CA, Sundar IK, Yao H, Gerloff J, Ossip DJ et al. (2015) Vapors produced by electronic cigarettes and E-Juices with flavorings induce toxicity, oxidative stress, and inflammatory response in lung epithelial cells and in mouse lung. *PloS ONE* 10: e0116732.
37. Pradeep AR, Ramchandraprasad MV, Bajaj P, Rao NS, Agarwal E (2013) Protein carbonyl: an oxidative stress marker in gingival crevicular fluid in healthy, gingivitis, and chronic periodontitis subjects. *Contemp Clin Dent* 4: 27-31.
38. Lee WH, Ong SG, Zhou Y, Tian L, Bae HR et al. (2019) Modeling Cardiovascular Risks of E-Cigarettes With Human-Induced Pluripotent Stem Cell-Derived Endothelial Cells. *J Am Coll Cardiol* 73: 2722-2737.

39. Farsalinos KE, Romagna G (2014) Cytotoxicity of cinnamon-flavored electronic: are the results truly applicable? *Toxicol In Vitro* 28: 1016-7.

40. Romagna G, Allifranchini E, Bocchietto E, Todeschi S, Esposito M et al. (2013) Cytotoxicity evaluation of electronic cigarette vapor extract on cultured mammalian fibroblasts (ClearStream-LIFE): comparison with tobacco cigarette smoke extract. *Inhal Toxicol* 25: 354-61.

41. Rubenstein DA, Hom S, Ghebrehiwet B, Yin W (2015) Tobacco and e-cigarette products initiate Kupffer cell inflammatory responses. *Mol Immunol* 67: 652-660

42. Ji EH, Sun B, Zhao T, Shu S, Chang CH et al. (2016) Characterization of electronic cigarette aerosol and its induction of oxidative stress response in oral keratinocytes. *PloS ONE* 11: e0154447.

43. Schober W, Szendrei K, Matzen W, Osiander-Fuchs H, Heitmann D et al. (2014) Use of electronic cigarettes (e-cigarettes) impairs indoor air quality and increases FeNO levels of e-cigarette consumers. *Int J Hyg Environ Health* 217: 628-637.

44. Hahn J, Monakhova YB, Hengen Y, Kohl-Himmelseher M, Schüssler J et al. (2014) Electronic cigarettes: overview of chemical composition and exposure estimation. *Tob Induc Dis* 12: 23.

45. Grana RA, Ling PM (2014) "Smoking revolution": A content analysis of electronic cigarette retail websites. *Am J Prev Med* 46: 395-403.

46. Jovanovic M, Jakovljevic M (2015) Regulatory issues surrounding audit of electronic cigarette charge composition. *Front Psychiatry* 6: 133.

47. Alawsi F, Nour R, Prabhu S (2015) Are e-cigarettes a gateway to smoking or a pathway to quitting. *Br Dent J* 219: 111.

48. Barrington-Trimis JL, Samet JM, McConnell R (2014) Flavorings in electronic cigarettes: an unrecognized respiratory health hazard? *JAMA* 312: 2493-2494.

49. Behar RZ, Davis B, Wang Y, Bahl V, Lin S et al. (2013) Identification of toxicants in cinnamon-flavored electronic cigarette refill fluids. *Toxicol In Vitro* 28: 198-208.

50. Clapp PW, Lavrich KS, van Heusden C, Lazarowski ER, Carson JL (2019) Cinnamaldehyde in Flavored E-Cigarette Liquids Temporarily Suppresses Bronchial Epithelial Cell Ciliary Motility by Dysregulation of Mitochondrial Function. *Am J Physiol Lung Cell Mol Physiol* 316: L470-L486.

51. Clapp PW, Pawlak EA, Lackey JT, Keating JE, Reeber SL et al. (2017) Flavored e-cigarette liquids and cinnamaldehyde impair respiratory innate immune cell function. *Am J Physiol Lung Cell Mol Physiol* 313: L278-L292.

52. Hickman E, Herrera CA, Jaspers I (2019) Common E-Cigarette Flavoring Chemicals Impair Neutrophil Phagocytosis and Oxidative Burst. *Chem Res Toxicol* 32: 982-985.

53. Bahl V, Lin S, Xu N, Davis B, Wang YH et al. (2012) Comparison of electronic cigarette refill fluid cytotoxicity using embryonic and adult models. *Reprod Toxicol* 34: 529-37.

54. Behar RZ, Luo W, Lin SC, Wang Y, Valle J (2016) Distribution, quantification and toxicity of cinnamaldehyde in electronic cigarette refill fluids and aerosols. *Tob Control* 25: 94-102.

55. Willershausen I, Wolf T, Weyer V, Sader R, Ghanaati S et al. (2014) Influence of E-smoking liquids on human periodontal ligament fibroblasts. *Head Face Med* 10: 39.

56. Otero CE, Noeker JA, Brown MM, Wavreil FD, Harvey WA et al. (2019) Electronic cigarette liquid exposure induces flavor□dependent osteotoxicity and increases expression of a key bone marker, collagen type I. *J Appl Toxicol* 39: 888-898.

57. Long GA (2014) Comparison of Select Analytes in Exhaled Aerosol from E-Cigarettes with Exhaled Smoke from a Conventional Cigarette and Exhaled Breaths. *Int J Environ Res Public Health* 11: 11177-11191.

58. Henningfield JE (1995) Nicotine medications for smoking cessation. *N Engl J Med* 333: 1196-1203.

59. Vansickel AR, Eissenberg T (2013) Electronic cigarettes: effective nicotine delivery after acute administration. *Nicotine Tob Res* 15: 267-270.

60. Farsalinos KE, Spyrou A, Tsimopoulou K, Stefopoulos C, Romagna G et al. (2014) Nicotine absorption from electronic cigarette use: comparison between first and new-generation devices. *Sci Rep* 4: 4133.

61. Vansickel AR, Cobb CO, Weaver MF (2010) A clinical laboratory model for evaluating the acute effects of electronic "cigarettes": nicotine delivery profile and cardiovascular and subjective effects. *Cancer Epidemiol Biomarkers Prev* 19: 1945-1953.

62. Simonavicius E, McNeill A, Shahab L, Brose LS (2019) Heat-not-burn tobacco products: a systematic literature review. *Tobacco control* 28: 582-594.

63. Oncken CA, Litt MD, McLaughlin LD, Burki NA (2015) Nicotine concentrations with electronic cigarette use: effects of sex and flavor. *Nicotine Tob Res* 17: 473-478.

64. Etter JF (2014) Levels of saliva cotinine in electronic cigarette users. *Addiction 109*: 825-829.

65. Marsot A, Simon N (2016) Nicotine and cotinine levels with electronic cigarette: a review. *Int J Toxicol* 35: 179-85.

66. https://www.cdc.gov/reproductivehealth/maternalinfanthealth/substance-abuse/e-cigarettes-pregnancy.htm#.

67. Suter MA, Mastrobattista J, Sachs M, Aagaard K (2015) Is there evidence for potential harm of electronic cigarette use in pregnancy? *Birth Defects Res A Clin Mol Teratol* 103: 186-195.

68. Holliday RS, Campbell J, Preshaw PM (2019) Effect of nicotine on human gingival, periodontal ligament and oral epithelial cells. A systematic review of the literature. *Journal of dentistry* 86: 81-88.

69. Frazer-Abel AA, Baksh S, Fosmire SP, Willis D, Pierce AM et al. (2004) Nicotine activates nuclear factor of activated T cells c2 (NFATc2) and prevents cell cycle entry in T cells. *J Pharmacol Exp Ther* 311: 758-769.

70. Levin L, Schwartz-Arad D (2005) The effect of cigarette smoking on dental implants and related surgery. *Implant Dent* 14: 357-363.

71. Rothem DE, Rothem L, Soudry M, Dahan A, Eliakim R (2009) Nicotine modulates bone metabolism-associated gene expression in osteoblast cells. *J Bone Miner Metab* 27: 555-561.

72. Flouris AD, Chorti MS, Poulianiti KP, Jamurtas AZ, Kostikas K et al. (2013) Acute impact of active and passive electronic cigarette smoking on serum cotinine and lung function. *Inhalation Toxicol* 25: 91-101.

73. Vardavas CI, Anagnostopoulos N, Kougias M, Evangelopoulou V, Connolly GN et al. (2012) Short-term pulmonary effects of using an electronic cigarette: impact on respiratory flow resistance, impedance, and exhaled nitric oxide. *Chest* 141: 1400-1406.

74. Orellana-Barrios MA, Payne D, Mulkey Z, Nugent K (2015) Electronic Cigarettes- A narrative Review for Clinicians. *Am J Med* 128(7): 674-681.

75. Dautzenberg B, Garelik D (2017) Patients with lung cancer: Are electronic cigarettes harmful or useful? *Lung Cancer* 105: 42-48.

76. Sussan TE, Gajghate S, Thimmulappa RK, Ma J, Kim J-H et al. (2015) Exposure to Electronic Cigarettes Impairs Pulmonary Anti-Bacterial and Anti-Viral Defenses in a Mouse Model. *PLoS ONE* 10(2): e0116861.

77. Lim HB, Kim SH (2014) Inhalation of e-cigarette cartridge solution aggravates allergen-induced airway inflammation and hyper-responsiveness in mice. *Toxicol Res* 30: 13-18.

78. Wu Q, Jiang D, Minor M, Chu HW (2014) Electronic cigarette liquid increases inflammation and virus infection in primary human airway epithelial cells. *PLoS ONE* 9: e108342.

79. Crotty AL, Enany S, Hwang H, Sladewski K, Nizet V (2014) Electronic cigarette vapor (ECV) exposure decreases Staphylococcus aureus susceptibility to macrophage and neutrophil killing. In A110. LATE BREAKING ABSTRACTS IN DISEASE SUSCEPTIBILITY AND PATHOGENESIS. American Thoracic Society. *Am J Respir Crit Care Med* 189: 6624.

80. Javed F, Kellesarian SV, Sundar IK, Romanos GE, Rahman I (2017) Recent updates on electronic cigarette aerosol and inhaled nicotine effects on periodontal and pulmonary tissues. *Oral Dis* 23: 1052-1057.

81. Bhatnagar A, Whitsel LP, Ribisl KM, Bullen C, Chaloupka F et al. (2014) Electronic cigarettes: a policy statement from the American Heart Association. *Circulation* 130: 1418-36.

82. http: //publications.iarc.fr/Book-And-Report-Series/Iarc-Monographs-On-The-Identification-Of-Carcinogenic-Hazards-To-Humans/Chemical-Agents-And-Related-Occupations-2012

83. Järup L (2003) Hazards of heavy metal contamination. *Br Med Bull* 68: 167-82.

84. Tierney PA, Karpinski CD, Brown JE, Luo W, Pankow JF (2016) Flavour chemicals in electronic cigarette fluids. *Tob Control* 25: 10-15.

85. Gerloff J, Sundar IK, Freter R, Sekera ER, Friedman AE, et al. (2017) Inflammatory response and barrier dysfunction by different e-cigarette flavoring chemicals identified by gas chromatography-mass spectrometry in e-liquids and e-vapors on human lung epithelial cells and fibroblasts. *Appl In Vitro Toxicol 3*: 28-40.

86. Benowitz NL (2014) Emerging nicotine delivery products. Implications for public health. *Ann Am Thorac Soc* 11: 231-235.

87. Stockley JA, Walton GM, Lord JM, Sapey E (2013) Aberrant neutrophil functions in stable chronic obstructive pulmonary disease: the neutrophil as an immunotherapeutic target. *Int Immunopharmacol 17*: 1211-7.

88. Das KK, Das SN, Dhundasi SA (2008) Nickel, its adverse health effects & oxidative stress. *Indian J Med Res* 128: 412-425

89. National Toxicology Programme (1996) NTP toxicology and carcinogenesis studies of nickel oxide (CAS no. 1313-99-1) in F344 rats and B6C3F1 mice (inhalation studies). *Natl Toxicol Program Tech Rep Ser* 451: 1-381

90. Pisinger C, Dossing M (2014) A systematic review of health effects of electronic cigarettes. *Prev Med* 69: 248-260.

91. Lippi G, Favaloro EJ, Meschi T, Mattiuzzi C, Borghi L, et al. (2014) E-cigarettes and cardiovascular risk: Beyond science and mysticism. *Semin Thromb Hemost* 40: 60-65.

92. Qasim H, Karim ZA, Rivera JO, Khasawneh FT, Alshbool FZ (2017) Impact of electronic cigarettes on the cardiovascular system. *J Am Heart Assoc* 6: e006353.

93. Morris PB, Ference BA, Jahangir E, Feldman DN, Ryan JJ, et al. (2015) Cardiovascular effects of exposure to cigarette smoke and electronic cigarettes: Clinical perspectives from the prevention of cardiovascular disease section leadership council and early career councils of the American college of cardiology. *J Am Coll Cardiol* 66: 1378-1391.

94. Ehle AL (1986) Lead neuropathy and electrophysiological studies in low level lead exposure: a critical review. *Neurotoxicology* 7: 203-216

95. Mason LH, Harp JP, Han DY (2014) Pb neurotoxicity: neuropsychological effects of lead toxicity. *Biomed Res Int* 1-8.

96. Silbergeld EK (1992) Mechanisms of lead neurotoxicity, or looking beyond the lamppost. *FASEB J* 6: 3201-3206

97. Apostolou A, Garcia-Esquinas E, Fadrowski JJ, McLain P, Weaver VM, et al. (2012) Second hand tobacco smoke: a source of lead exposure in US children and adolescents. *Am J Public Health* 102: 714-722.

98. Fadrowski JJ, Navas-Acien A, Tellez-Plaza M, Guallar E, Weaver VM, et al. (2010) Blood lead level and kidney function in US adolescents: the third National Health and Nutrition Examination Survey. *Arch Intern Med* 170: 75-82.

99. Harrison R, Hicklin D Jr. (2016) Electronic cigarette explosions involving the oral cavity. *J Am Dent Assoc* 147: 891-896.

100. Rouabhia M, Park HJ, Semlali A, Zakrzewski A, Chmielewski W, et al. (2017) E-vapor induces an apoptotic response in human gingival epithelial cells through the caspase- 3 pathway. *J Cell Physiol* 232: 1539-1547.

101. Sundar IK, Javed F, Romanos GE, Rahman I (2016) E-cigarettes and flavorings induce inflammatory and pro-senescence responses in oral epithelial cells and periodontal fibroblasts. *Oncotarget* 7: 77196-77204.

102. Sancilio S, Gallorini M, Cataldi A, Giacomo V (2016) Cytotoxicity and apoptosis induction by e-cigarette fluids in human gingival fibroblasts. *Clin Oral Invest* 20: 477-483.

103. Cuadra GA, Smith MT, Nelson JM, Loh EK, Palazzolo DL (2019) A Comparison of Flavorless Electronic Cigarette-Generated Aerosol and Conventional Cigarette Smoke on the Survival and Growth of Common Oral Commensal Streptococci. *Int J Environ Res Public Health 16*: 1669

104. Kim SA, Smith S, Beauchamp C, Song Y, Chiang M, et al. (2018) Cariogenic potential of sweet flavors in electronic-cigarette liquids. *PloS ONE 13*: e0203717.

105. Alanazi H, Semlali A, Chmielewski W, Rouabhia M (2019) E-Cigarettes Increase Candida albicans Growth and Modulate its Interaction with Gingival Epithelial Cells. *Int J Environ Res Public Health* 16: 294.

106. ALHarthi SS, BinShabaib M, Akram Z, Rahman I, Romanos GE, et al. (2019) Impact of cigarette smoking and vaping on the outcome of full-mouth ultrasonic scaling among patients with gingival inflammation: a prospective study. *Clin Oral Investig* 23: 2751-2758.

107. BinShabaib M, ALHarthi SS, Akram Z, Khan J, Rahman I (2019) Clinical periodontal status and gingival crevicular fluid cytokine profile among cigarette-smokers, electronic-cigarette users and never-smokers. *Arch Oral Biol* 102: 212-217.

108. ArRejaie AS, Al-Aali KA, Alrabiah M, Vohra F, Mokeem SA, et al. (2019) Proinflammatory cytokine levels and peri-implant parameters among cigarette smokers, individuals vaping electronic cigarettes, and non-smokers. *J Periodontol* 90: 367-374.

109. Bardellini E, Amadori F, Conti G, Majorana A (2018) Oral mucosal lesions in electronic cigarettes consumers versus former smokers. *Acta Odontol Scand* 76: 226-228.

110. Leigh NJ, Lawton RI, Hershberger PA, Goniewicz ML (2016) Flavouring significantly affect inhalation toxicity of aerosol generated from electronic nicotine delivery systems (ENDS). *Tob Control* 25: 81-87.

111. Mokeem SA, Abduljabbar T, Al□Kheraif AA, Alasqah MN, Michelogiannakis D (2019) Oral Candida carriage among cigarette□and waterpipe□smokers, and electronic cigarette users. *Oral diseases 25*: 319-326.

112. Hsia CC, Sun TT, Wang YY, Anderson LM, Armstrong D, et al. (1981) Enhancement of formation of the esophageal carcinogen benzylmethylnitrosamine from its precursors by Candida albicans. *Proc Natl Acad Sci USA* 78: 1878-1881.

113. Banoczy J, Gintner Z, & Dombi C (2001) Tobacco use and oral leukoplakia. *J Dent Educ* 65: 322-327.

114. Bennet KR, Reade PC (1982) Salivary immunoglobulin A levels in normal subjects, tobacco smokers, and patients with minor aphthous ulceration. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 53: 461-465.

115. Berman J, Sudbery PE (2002) Candida Albicans: a molecular revolution built on lessons from budding yeast. *Nat Rev Genet* 3: 918-930.

116. Tommasi S, Caliri AW, Caceres A, Moreno DE, Li M, et al. (2019). Deregulation of biologically significant genes and associated molecular pathways in the oral epithelium of electronic cigarette users. *Int J Mol Sci* 20: 738.

117. Hajek P, Phillips-Waller A, Przulj D, Pesola F, Myers Smith K, et al. (2019) A Randomized Trial of E-Cigarettes versus Nicotine-Replacement Therapy. *N Engl J Med* 380: 629-637.

118. Drouin O, McMillen RC, Klein JD, Winickoff JP (2018) E-cigarette advice to patients from physicians and dentists in the United States. *Am J Health Promot 32*: 1228-1233.

119. Martín Carreras□Presas C, Naeim M, Hsiou D, Somacarrera Pérez ML, Messadi DV (2018) The need to educate future dental professionals on E□cigarette effects. *European Journal of Dental Education 22*: e751-e758.

120. Cummings KM, Morris PB, Benowitz NL (2018) Another Article About E□ Cigarettes: Why Should I Care? *J Am Heart Assoc* 7: e009944.

121. Bunnell RE, Agaku IT, Arrazola RA, Apelberg BJ, Caraballo RS, et al. (2015) Intentions to smoke cigarettes among never-smoking US middle and high school electronic cigarette users: National Youth Tobacco Survey, 2011-2013. *Nicotine Tob Res* 17: 228-235.

122. Gmel G, Baggio S, Mohler-Kuo M, Daeppen JB, Studer J (2016) E-cigarette use in young Swiss men: is vaping an effective way of reducing or quitting smoking? *Swiss Med Wkly* 146: w14271.

123. Wills TA, Sargent JD, Knight R, Pagano I, Gibbons FX (2016) E-cigarette use and willingness to smoke: a sample of adolescent non-smokers. *Tob Control* 25: e52-e59.

124. Cobb NK, Abrams DB (2011) E-cigarette or drug-delivery device? Regulating novel nicotine products. *N Engl J Med* 365: 193-195.

125. Hess IM, Lachireddy K, Capon A (2016) A systematic review of the health risks from passive exposure to electronic cigarette vapour. *Public Health Res Pract* 26: e2621617.

126. Torjesen I (2014) E-cigarette vapour could damage health of non-smokers. *BMJ* 6882.

127. Tayyarah R, Long GA (2014) Comparison of select analytes in aerosol from e-cigarettes with smoke from conventional cigarettes and with ambient air. *Regul Toxicol Pharmacol* 70: 704-710.

128. Ruprecht AA, De Marco C, Pozzi P, Munarini E, Mazza R, et al. (2014) Comparison between particulate matter and ultrafine particle emission by electronic and normal cigarettes in real-life conditions. *Tumori* 100: e24-e27.

129. Czogala J, Goniewicz ML, Fidelus B, Zielinska-Danch W, Travers MJ, et al. (2014) Secondhand exposure to vapors from electronic cigarettes. *Nicotine Tob Res* 16: 655-662.

130. Goniewicz ML, Gupta R, Lee YH, Reinhardt S, Kim S, et al. (2015) Nicotine levels in electronic cigarette refill solutions: A comparative analysis of products from the US, Korea, and Poland. *Int J Drug Policy* 26: 583-588.

131. Riker CA, Lee K, Darville A, Hahn EJ. (2012) E-cigarettes: promise or peril? *Nurs Clin North Am* 47: 159-171.

132. Springer R (2014) Electronic cigarettes - patient safety concerns. *Plast Surg Nurs* 34: 165-166.

133. Young-Wolff KC, Karan LD, Prochaska JJ (2015) Electronic cigarettes in jails: a panacea or public health problem? *JAMA Psychiatry* 72(2): 103-104.

134. Saffari A, Daher N, Ruprecht A, De Marco C, Pozzi P, et al. (2014) Particulate metals and organic compounds from electronic and tobacco-containing cigarettes: comparison of emission rates and secondhand exposure. *Environ Sc Process Impacts* 16(10): 2259-2267.

135. England LJ, Bunnell RE, Pechacek TF, Tong VT, McAfee TA (2015) Nicotine and the developing human: a neglected element in the electronic cigarette debate. *Am J Prev Med* 49: 286-293

136. Bayly JE, Bernat D, Porter L, O'Dare K, Choi K (2019) Prevalence and characteristics of secondhand smoke and secondhand vapour exposure among youth. *Tob Control* 28: 305-310.