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Review Article

A review of the dermatological manifestations associated with e-cigarettes and vaping

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E-cigarette use among American middle and high school students has increased tremendously in the past decade. This is alarming, as e-cigarette users and others around them are at risk of inhalation of toxic substances including heavy metals, volatile organic compounds, and ultrafine particles that can deposit deep into the lungs. Additionally, there are dermatologic sequalae including contact dermatitis, impaired wound healing, and oral mucosal lesions. In this review we characterize the dermatological burden of e-cigarettes and vaping.

INTRODUCTION

When e-cigarettes were introduced to the US market in 2006 and 2007,[1,2] e-cigarettes were marketed as a healthier alternative to smoking cigarettes and a step to quitting smoking altogether.[1-3] Unfortunately, e-cigarettes rarely served this intended purpose and instead exposed an innumerable number of adolescents to nicotine's deleterious effects.[1-4] The Center for Disease Control and Prevention (CDC) reports that e-cigarette use among American middle and high school students increased 900% from 2011 to 2015, and as of 2018, more than 3.6 million U.S. youth, including 1 in 5 high school students and 1 in 20 middle school students currently use e-cigarettes.[5] The CDC also cautions that early exposure to nicotine during adolescence, a critical time of brain development, can impact learning, memory, and attention.[5] Additionally, nicotine use during the teenage years increases the risk of future addiction to other drugs.[5] Furthermore, e-cigarette users and others around them are at risk of inhalation of toxic substances, including heavy metals, volatile organic compounds, and ultrafine particles that will deposit deep into the lungs.[5] These substances, along with nicotine, link e-cigarettes to the development of obstructive lung diseases and lung cancer.[3] While the detrimental consequences of e-cigarette consumption on lung tissue have been researched and continue to gain well-deserved attention,[3] the impact of e-cigarettes on the skin is less studied.[6] Considering the monumental rise of e-cigarettes in adolescents,[5] while bearing in mind that a significant portion of most dermatology practices includes the treatment of pubertal acne,[7] dermatologists can play a critical role in educating youths on the damaging health repercussions of e-cigarettes and in promoting smoking cessation.[6] This review aims to characterize the dermatological burden of e-cigarettes and vaping.

CELLULAR BASIS FOR DAMAGE

Numerous studies have demonstrated that a primary mechanism for e-cigarette-induced bodily harm is the development of reactive oxygen species (ROS) in endothelial cells.[8-11] At the biological level, e-cigarettes produce reactive oxygen species, damage DNA, and promote the preprogrammed apoptotic and necrotic pathways in cells.[8] Endothelial cell dysfunction is the constitutional basis of e-cigarette-related dermatological damage.[6,8-10] A healthy endothelium is vital to the homeostatic functioning of the skin[12] and is dependent on vascular tone and regular blood flow, among others.[6,8,10,12] The free radicals from e-cigarettes increase plasma viscosity disrupting traditional blood flow mechanics.[6,10] At the same time, nicotine causes atypical, unorganized angiogenesis, evident by smokers having increased expression of vascular endothelial growth factor (VEGF).[6,10]

ALLERGIC CONTACT DERMATITIS

There have been cases of allergic contact dermatitis associated with e-cigarette use, mainly due to the nickel con-

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tent in e-cigarettes.[13,14] Another possible pathogenesis for the evolution of e-cigarette-derived allergic contact dermatitis is the spillage of e-cigarette liquid which contains menthol.[15] E-cigarettes also contain hydroxycitronellal, iodopropynyl butyl carbamate, and polyethylene glycol, which are well-known culprits of contact dermatitis.[16-20] The way the patient holds the vaping device leads to the development of allergic contact dermatitis, likely due to palmar sweat corroding the device, exposing the nickel to the epidermis.[13,14] The most common location for e-cigarette-induced allergic contact dermatitis is the palms, usually the dominant hand, consistent with this anatomic location receiving the most exposure to the metal vaping device.[13-15] The second most common location for vaping-induced allergic contact dermatitis is the face and superior neck region, customarily along with hand dermatitis.[13,16,18,20] The clinical symptoms of this contact dermatitis include pruritic, erythematous scaly patches with or without lichenification.[13-16,18,20]

E-cigarettes are popular in the younger population due to their many flavorings, such as cinnamon.[21] However, these e-cigarette flavorings contain compounds such as eugenol and cinnamaldehyde, two well-known skin sensitizers.[21] The development of allergic contact dermatitis from these sensitizers in vapers is thought to have a similar pathogenesis to allergic contact dermatitis due to occupational exposures to low-molecular-weight chemicals.[21] In vitro studies have demonstrated that cinnamaldehyde suppresses immune responses in macrophages and neutrophils, impairing the innate immunity and perhaps lending to its efficacy as a sensitizer.[21,22] Additionally, the application of electronic cigarette refill fluids to human skin models has demonstrated increased oxidative stress in human keratinocytes and the secretion of pro-inflammatory cytokines including IL-1α and MMP-9, suggesting that a dysfunctional skin barrier could contribute to e-cigarette-induced allergic contact dermatitis.[23]

While some patients who developed allergic contact dermatitis from e-cigarettes report a past history of contact dermatitis,[13-16,18,20] a lack of a prior positive medical history does not protect against the development of vaping-induced contact dermatitis.[13-16,18,20] In teenagers presenting with dominant-hand dermatitis with or without facial and neck dermatitis, e-cigarette-induced contact dermatitis should be included in the differential with possible patch testing for nickel and other cosmetic allergens if deemed necessary.

ATOPIC DERMATITIS

There is an established link between smoking and an increased risk for atopic dermatitis (AD), even in adolescents.[24,25] While there are no extensive studies on the association of e-cigarettes with allergic diseases, the available literature states that e-cigarette users develop more asthmatic symptoms than non-smokers.[25,26] Furthermore, adolescents who use e-cigarettes are at increased risk of developing the "atopic march" consisting of the triad of asthma, atopic dermatitis, and allergic rhinitis compared to non-smokers.[25] The atopic march in adolescents is associated with an increase in physician appointments, visits to the emergency room, and prescription medicine load.[25] Additionally, while e-cigarette use increases the risk for the development of the "atopic march," even using any tobacco product ever is significantly associated with a sole diagnosis of AD in teenagers.[25] In fact, in this patient population, AD commonly manifests as the start of the "atopic march."[25] A possible pathophysiology of e-cigarette-induced AD hypothesizes that inhalation of e-cigarette aerosols leads to local cutaneous sensitization, which activates the systemic immune response: sensitized T cells migrate into the mucous membranes of the nose and lung throughout the circulatory system.[25] These sensitized T cells then activate eosinophils and epithelial cells, promoting Immunoglobulin E (IgE) production and the proliferation of mast cells and smooth muscle.[25] While this is a plausible theory, additional studies and research are needed to fully elucidate the mechanism of e-cigarette-associated allergic damage.[25] In an adolescent presenting with a sudden onset of atopic dermatitis followed by asthma and allergic rhinitis, e-cigarette-induced sensitization should be considered.

BURNS

E-cigarette burns likely originate from lithium-ion battery dysfunction or metal item induced short-circuiting.[27,28] E-cigarette burns from a lithium-ion battery malfunction result in a fire or explosion that damages the patient's skin.[27,28] The lithium-ion battery malfunction is hypothesized to occur from thermal runaway: when the patient inhales the aerosols, the reaction rate and subsequent temperature increase inside the device cause the charged volatile organic components to short circuit.[27,28] Another theory is that when patients carry metallic objects in their pockets, such as coins, keys, or buttons, these come into contact with the e-cigarette, producing a short circuit and causing the battery to overheat.[28] This theory is supported by the most common location of e-cigarette burns being the lower limb.[27,28] In most reported cases, the patients that experience the most e-cigarette-related burns are males in their 20s and 30s.[27,28] The most common type of burns are flame burns, followed by chemical alkaline burns.[28] The depth of these burns varies somewhat, from superficial to deep, with a slight predominance in mixed-depth burns.[27,28] Many of these burns require skin graft reconstruction,[28] and the complications of burns are not slight: hypovolemic shock, sepsis, acute respiratory dress syndrome, and renal failure.[29]

WOUND HEALING

While traditional cigarettes have been highly associated with impairments in wound healing,[30] there is a paucity of literature concerning the effects of e-cigarettes on wound healing. Preliminary literature has found a high detrimental potency resulting from e-cigarette use in rats.[31] In endothelial cells, flavored and nicotine-containing e-cigarettes demonstrate endothelial dysfunction through excess

reactive oxygen species, decreased nitric oxide bioavailability, increased endothelial cell apoptosis, and impairments in angiogenesis and wound healing, especially under diabetic conditions.[32] An important takeaway from these findings is its relevance to clinical practice, especially before surgery: many patients may not report that they are smokers because e-cigarettes are not "technically cigarettes" to many.[31-33] However, e-cigarettes are highly associated with impairments in wound healing and a higher percentage of poor surgical outcomes, including skin necrosis and vasospasm.[33] Dermatologists should be aware of these effects and caution their patients accordingly.

ORAL MUCOSAL LESIONS

As the oral mucosa is the first place in contact with the inhaled vapors from e-cigarettes, the oral mucosa is highly prone to damage.[34-38] Various lesions and mucosal impairments are seen in e-cigarette users,[34-38] and dermatologists should be aware of these lesions to counsel patients. E-cigarette users are prone to the development of certain disorders as compared to former smokers: nicotine stomatitis, hyperplastic candidiasis, angular cheilitis, and black hairy tongue (BHT).[34,37,38]

NICOTINE STOMATITIS

Nicotine stomatitis, also known as smoker's keratosis, is an irritating condition of the oral mucosa characterized clinically by diffuse gray or white color change to the hard plate that may progress to scattered mucosal thickening and fissuring resulting in a "cracked mud" appearance.[38] The keratinization may also be visualized as raised red dots surrounded by white keratotic rings.[37] The pathophysiology is incompletely understood, but one possible theory suggests that nicotine stomatitis results from a high amount of heat being concentrated in the mouth due to smoking rather than from the explicit noxious effects of nicotine or the other products of e-cigarettes.[38] On the contrary, another theory postulates that the specific contents of e-cigarettes, including tobacco containing nicotine, artificial flavors, propylene glycol, and glycerol, are directly cytotoxic to the oral mucosa and cause keratinization as a possible protective mechanism to prevent further damage.[37]

HYPERPLASTIC CANDIDIASIS

Hyperplastic candidiasis in e-cigarette users most commonly presents in the oral mucosal retro-commissural area as white patches.[37,38] Hyperplastic candidiasis can be accompanied by a number of underlying co-morbidities, including diabetes mellitus and an immunocompromised state.[38] The underlying pathology of the growth of candida in the oral mucosa is speculated to involve a change in alkaline pH to acidic.[37,38] Chemical compounds in e-cigarettes degrade salivary protective factors responsible for an alkaline pH, such as lactoferrin, lactoperoxidase, and immunoglobulins.[37] Candida can then proliferate in acidic mucosa.[37,38]

BLACK HAIRY TONGUE

Black Hairy Tongue (BHT), also known as lingua villosa nigra, is a benign disorder that presents with desquamation of the dorsal aspect of the tongue.[38] The desquamation of the tongue is the pathological basis of this disorder: desquamation leads to elongation of the filiform papillae (taste buds) and proliferation of porphyrin-producing chromogenic bacteria, further producing a color change in the tongue.[38] BHT is thought to be directly linked to e-cigarettes, as demonstrated by the reversal of tongue color with cessation of vape products and subsequent return of color changes with resumption of e-cigarettes.[38] The primary inciting factor, the desquamation of the dorsal tongue, is suspected to originate from the e-cigarette-associated pH change.[37,38] Other mucosal damage is thought to result from e-cigarette-induced mucosal drying, higher intraoral temperatures, local alterations of membrane barriers, a change in immune response, or a modified resistance to infectious agents.[37,38]

OTHER MUCOSAL LESIONS

E-cigarettes are associated with other oral cavity complications, including lichen planus[37,38] and acute epiglottitis.[36] The classic appearance of lichen planus is Wickham striae: spreading white-gray papules composing a delicate, lacy reticular pattern.[38] E-cigarette-induced lichen planus is thought to be more of an oral lichenoid reaction based on mucosal biopsies rather than pure lichen planus; however, this is very difficult to distinguish clinically.[38] Mucosal lesions from e-cigarette users demonstrate a florid lichenoid reaction consistent with hyperkeratosis and lichenoid inflammation.[38] Oral lichenoid reactions may be a form of allergic contact dermatitis resulting from the propylene glycol content in e-cigarettes; however, data is lacking to confirm this theory entirely.[38] Another theory is the high presence of gold in e-cigarettes.[39] Some research has suggested that although the presence of gold in dental fillings itself is not associated with an increased risk of oral lichen planus, when dissimilar metals such as gold and amalgam are in contact for long periods of time, the risk for lichen planus is increased.[40]

Vaping has been noted to cause acute epiglottitis, a life-threatening airway obstruction associated with significant respiratory distress.[36] The mechanism of injury in acute epiglottitis involves epithelial cell damage followed by a subsequent inflammatory response evident by in vitro studies with e-cigarette vapor extract on human vocal fold mucosal cells.[36]

Various studies have demonstrated that e-cigarettes contain less arsenic than conventional cigarettes with e-cigarette users subsequently having lower rates of squamous cell carcinoma (SCC) than cigarette smokers.[41] Despite lower prevalence of SCC in e-cigarette users, an important point remains that the FDA has not issued any standards on e-cigarettes. Thus, the true levels of arsenic remain unknown.[42] While SCC is often thought of as a cancer of older adults, young patients are not exempt from this cancer. As an example, a 5-year-old patient was reported to

have oral SCC. Thus, dermatologists should be vigilant for such a development in their younger patients.[43]

PALMOPLANTAR PSORIASIS/PALMOPLANTAR PUSTULOSIS

Numerous studies have demonstrated a strong association between smoking and palmoplantar pustulosis (PPP), sometimes considered a subtype of psoriasis with many small, hyperkeratotic or pustular lesions primarily concentrated on the palms and soles.[44-50] One study found that nearly 95% of patients with PPP had a history of smoking or were smokers when PPP presented.[44] There is also substantial evidence to suggest that smoking cessation along with conventional clinical management improves symptoms of PPP compared to typical clinical therapy alone,[44] as patients with severe PPP have the highest pack-year smoking scores.[45] Nicotine from e-cigarettes is involved in the interplay of smoking and PPP via two mechanisms: increased cornification and increased neutrophilic inflammation.[44-50]

First, research proposes that nicotine increases cornification of keratinocytes in sweat glands.[44,49] Cornification is known as the slow, coordinated non-apoptotic programmed cell death of keratinocytes that leads to a formation of dead cells (corneocytes) to create a physical barrier for the skin.[51] Furthermore, the intraepidermal sweat duct (acrosyringium) of eccrine sweat glands appears to be the leading site of inflammation in PPP, as this is where vesicles and pustules form.[44,49] When comparing the palmar skin of PPP in smokers and non-smokers, the palmar skin of smokers revealed an abnormal expression of the ◈-7 subunit of keratinocyte nicotinic acetylcholine receptor, the receptor responsible for terminal differentiation of keratinocytes.[44,49,50] Deficient terminal differentiation of the keratinocytes surrounding eccrine sweat glands leads to impaired cutaneous homeostasis suggesting that this process might be the inciting factor in e-cigarette-induced PPP.[44,49]

Second, nicotine has shown to stimulate neutrophils to produce interleukin 8 (IL-8), otherwise known as the neutrophilic chemotaxis factor.[44,49] Neutrophil migration leads to leukocytosis in sweat glands and subsequent inflammation resulting in the symptoms of PPP.[44,49]

Aside from IL-8, the smoke extract from e-cigarettes may directly lead to the synergistic release of pro-inflammatory interleukins, including IL-17 and IL-36.[48,49,52] Tobacco products found in e-cigarettes are also thought to play a role in PPP by altering the cutaneous microbiome, as smoking directly increases the production of *Staphylococcus aureus*.[48]

CONCLUSION

The supreme rise of e-cigarettes in the past twenty years has had far-reaching consequences on the health of society, especially adolescents.[1-5] While the effects of e-cigarettes on lung tissue has been appreciated and accepted, the consequences of e-cigarette on the skin have been more elusive.[6] From the available literature, e-cigarettes presumably cause cutaneous damage by instigating endothelial cell dysfunction via generating reactive oxygen species and promoting pro-apoptotic pathways.[6,8-10] Allergic contact dermatitis deriving from e-cigarettes is likely mainly due to nickel, with polyethylene glycol and other cosmetic fragrances playing a more minor role.[13-20] E-cigarettes can increase the risk of the "atopic march" and the sole risk of atopic dermatitis, probably from sensitizing cutaneous T cells.[24-26] E-cigarettes and vape products can also cause various burns resulting from the short-circuiting of the smoking apparatus, either due to the lithium battery overheating or from the device contacting other metal products typically contained in the trousers of patients.[27,28] Aside from burns, e-cigarettes also significantly impair wound healing.[30-33] E-cigarettes also lead to several mucosal disorders, including nicotine stomatitis, hyperplastic candidiasis, lichenoid reactions and black hairy tongue.[37,38] Finally, e-cigarettes are highly associated with palmoplantar psoriasis through diverse cellular processes.[44-50,52]

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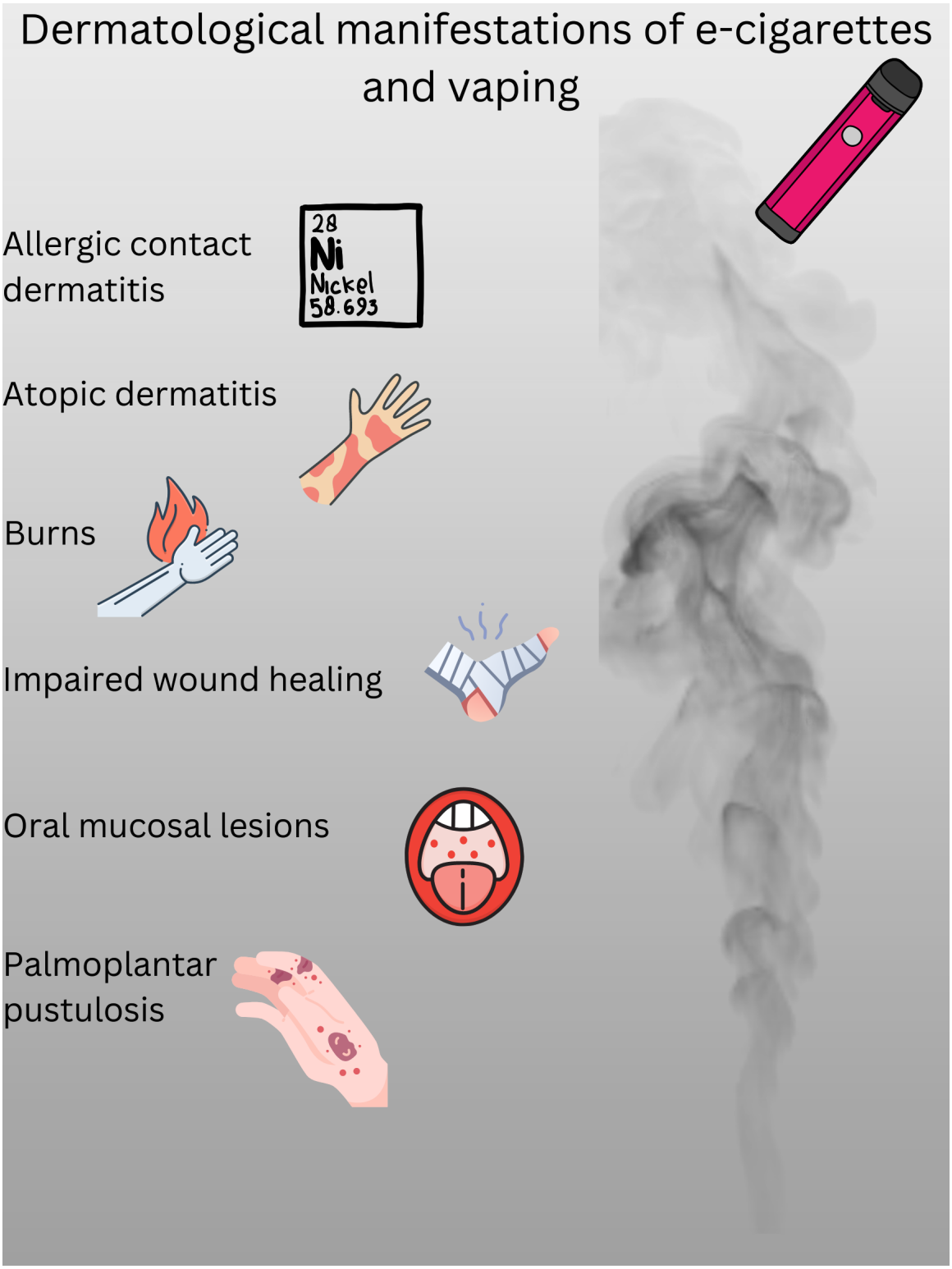

Figure 1. Summary of the dermatological manifestations associated with e-cigarettes

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