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Understanding the Relationship Between Smoking and Hidradenitis Suppurativa

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ABSTRACT Hidradenitis suppurativa (HS) is a chronic skin disease affecting hair follicles in intertriginous areas, characterized by deep, recurrent, painful nodules and abscesses, fistulae, sinus tracts, and scarring. With a prevalence of 1-4%, HS is not an uncommon disease. Several risk factors have been linked with the development of HS, such as genetic predisposition, smoking, and obesity, leading to the hypothesis that HS develops as a result of environmental triggers in a genetically susceptible individual. Smoking has been recognized as one of the environmental factors with the most impact on HS. This review aims to provide a comprehensive and holistic view on how smoking habits affect the incidence, severity, treatment, and pathophysiology of HS. A growing body of published literature has reported the association between smoking and HS, despite limitations in proving the causal relationship due to the retrospective design of the available studies. There is a consensus that patients with HS who are active smokers have a higher number of affected body areas than patients with HS who do not smoke or have stopped smoking. Similarly, it is recommended for patients with HS to discontinue tobacco use because of its association with weaker treatment response. Studies on the pathophysiological mechanism of smoking on the skin show that tobacco smoke with many of its chemicals as well as nicotine promote the proinflammatory cytokines found in HS lesions, activate the nicotinic acetylcholine (nAChRs) and aryl hydrocarbon receptors (AHRs), and further suppress Notch signaling pathway.

KEY WORDS: hidradenitis suppurativa, acne inversa, smoking, tobacco, cigarette

INTRODUCTION

Hidradenitis suppurativa (HS) is a chronic, relapsing, inflammatory skin disease that appears as a result of follicular occlusion and secondary rupture of the sebofollicular junction of folliculopilosebaceous units (FPSUs). Consequently, an inflammatory cascade occurs, presenting as recurrent, painful, and inflamed nodules that often rupture and leak purulent material (1). The chronic timeline of the disease leads

to the progression of nodules into abscesses, epithelialized sinuses, fistulae, and characteristic "rope-like" scarring (2).

HS clinically presents at several predilection sites, rich in apocrine glands, such as the axillae, perianal, and perineal regions. However, other areas can often be involved, such as the neck, retroauricular area, back, inner thighs, scrotum or labia, and the inframammary and mammary region in women. In women, inguinal and mammary regions are more commonly affected, while the anogenital area is more often affected in men (1). The early-stage diagnosis of hidradenitis suppurativa is often missed due to patients first presenting to emergency wards or surgical departments and the general lack of awareness of the severity of the condition.

The prevalence of hidradenitis suppurativa has been estimated at 1-4% in the general population (1). It affects young adults in their early twenties with an average disease onset at 21.8 years of age. HS is more frequent among women, except in the age group above 50 years, because in women the condition tends to subside after menopause.

Several risk factors have been linked with the development of HS, such as genetic predisposition, smoking, and obesity, leading to the hypothesis that HS develops as a result of environmental triggers in a genetically susceptible individual. Among the environmental factors playing a role in HS, smoking has been extensively researched as dermatologists and scientists struggle to determine the relationship between smoking and HS. This review article aims to summarize the growing body of literature on smoking and HS and to define the role of smoking in the development of HS.

METHODOLOGY

An extensive literature review was conducted of the PubMed and Web of Science databases, as well as a search on Google Scholar. Using the keywords (hidradenitis suppurativa, acne inversa, smoking, tobacco, cigarette), we analysed original scientific articles, review articles, and letters to the editors.

THE RELATIONSHIP BETWEEN SMOKING AND HIDRADENITIS SUPPURATIVA: FROM KARL MARX TO MODERN ERA

Little did Karl Marx know that his smoking habits and skin condition would be in the center of dermatologists' debate over the relationship between smoking and HS. The debate over the causes of Karl Marx's skin condition started in 2007 when Sam Shuster published that Marx's incapacitating skin disease was likely hidradenitis suppurativa (3). Since Marx was a chronic heavy smoker, dermatologists were quick to point out that smoking caused one of the most influential thinkers of the nineteenth century to develop a debilitating skin disease, which affected his life and work (4). Others were horrified by the idea of using Karl Marx, one of the symbols of scientific rationalism, to causally link smoking and HS amidst the lack of statistical evidence of a causal relationship (5). There have been several studies assessing the relationship between smoking and HS even before Sam Shuster's essay on Karl Marx. As early as 1997, the first studies reported the observation of a high prevalence of smokers among patients with HS. In 1997, Bassukas and Hundeiker suggested that toxic tobacco smoke might contribute to the pathogenesis of HS (6).

Konig *et al.* assessed the influence of smoking habits among 84 patients with HS and found out that 88.9% of their patients with HS were active smokers, which was a significantly higher rate than the rate of active smokers in the matched-pair control group (7). They further elaborate that it seems to be a rare event that a never-smoker suffers from HS. Happle and Konig's later work from 2011 suggests the more specific term "smoker's boils" for HS lesions of patients who are smokers, elaborating that the renaming would allow for a correct diagnosis at the initial stage of the disease. Such a proposal came after several close statistical relationships between HS and smoking were reported in several studies (8,9). Newer research methods, such as radioimmunoassay, have added to the growing evidence showing that both active and passive smokers excrete considerable amounts of nicotine with their sweat (10).

A recent study that investigated HS incidence among tobacco smokers in a large, diverse cohort of 50 million patients across the U.S. showed that the odds of a new diagnosis of HS were increased by 90% among those who smoked tobacco (11).

However, several articles have also been published that downplay the importance of smoking as a risk or triggering factor for HS (12,13). In a French analysis of 302 medically assessed patients and 67 self-diagnosed patients with HS, current smokers had 12.5- and 4-times higher odds of having HS, respectively (14). However, a history of previous smoking was not associated with HS, suggesting that smoking habits may have been a consequence of the disease. Some authors have even gone further in questioning the work of Garg *et al.*, implying that their conclusions about the relationship between smoking and HS go well beyond what is permissible from the evidence

(15). Shuster acknowledges the higher percentage of active smokers among patients with HS but states that this fact does not allow the presumption of causality, accusing some authors of misapplication of associative epidemiology to etiology (5). Several other authors also questioned whether smoking increases the risk of developing HS *de novo* or is instead a consequence of the disease (high rates of depression and anxiety among patients with HS; HS influencing individuals to smoke tobacco to cope with the psychological impact of the disease) (16,17).

While there are inherent limitations in retrospective studies linking smoking and HS, including the ability to establish a real temporal relationship, there is a growing body of literature establishing the association between smoking and HS. As clinicians, however, it is our responsibility to inform every patient with a dermatological condition about the harmful effects of smoking on the skin.

TOBACCO SMOKING AND THE SEVERITY OF HIDRADENITIS SUPPURATIVA

The role of lifestyle factors on HS, such as tobacco smoking, deserves special consideration as they are modifiable by the patients themselves and could represent an opportunity for a successful self-mitigating course for disease remission.

Available studies show conflicting results on the association of smoking with HS severity. Matusiak *et al.*, in an investigation of 54 Polish patients, found no significant correlation between smoking and clinical severity based on the Hurley scale or with an earlier onset of the disease. However, there was a significant difference between the group of active smokers and nonsmokers concerning the number of skin areas affected by HS lesions (18).

Dessinioti *et al.*, in their study of 133 patients, found that the severity of HS according to Hurley staging was not associated with current or former smoking compared with non-smoking. However, similar to the findings of Matusiak *et al.*, they reported that current or former smoking was associated with the number of affected body areas, i.e. with an increased risk for active smokers to have more than two body areas affected compared with non-smokers (19).

A study of 115 patients with HS conducted by Sartorius *et al.* reported higher severity HS (according to the modified Hidradenitis Suppurativa Score (HSS)) in smokers compared with nonsmokers (20). This finding might suggest that the recently developed, more detailed HSS can capture more of the essential clinical information on the patient's habits than Hurley staging.

Regarding the cessation of smoking and the remission of HS, Matusiak *et al.* observed no significant alteration in the clinical manifestations of HS in patients who ceased to smoke (21). However, in study on 212 patients by Kromann *et al.*, no smoking was 2.8 times more likely to be associated with self-reported remission compared to active smoking (21).

TOBACCO SMOKING AND TREATMENT RESPONSE

While there are conflicting studies on the link between tobacco smoking and HS, both regarding occurrence and disease severity, there is a growing body of evidence suggesting that smoking status influences response to treatment. Kroman *et al.* showed that 66% of their patients who reported remission were nonsmokers and that those who did not smoke were two times more likely to self-report remission compared with smokers (21).

A study by Denny *et al.* found that nonsmokers or former smokers were almost three times more likely to have an improvement in their disease compared with current smokers by being more likely to positively respond to conventional medical therapies, including antibacterial washes/creams/lotions, topical and oral antibiotics, and intralesional corticosteroids (22).

There is a consensus suggesting physicians strongly recommend their patients with HS to discontinue tobacco use because of its association with weaker treatment response.

THE PATHOMECHANISM OF SMOKING EFFECTS ON THE SKIN HELPS US UNDERSTAND THE INTERESTING CLINICO-EPIDEMIOLOGICAL HYPOTHESIS ON THE LINK BETWEEN SMOKING AND HS

In trying to determine the specific type of relationship between smoking and HS (epidemiological or causal), we need to delve into the pathomechanisms of HS and how nicotine and chemicals from tobacco smoke could induce the formation of HS lesions.

There is a growing body of literature on the pathophysiology of HS suggesting multifactorial causes to the emergence of HS phenotype. Cytokines involved in HS pathogenesis include interleukin (IL)-1β, IL-17, IL-10, IL-23, and, to a lesser extent TNF-α (23). Their potent pro-inflammatory capacity drives the influx of immune cells and triggers the inflammatory response cascade. Studies of the genetic aberrations in HS found that the loss of function mutations in the gamma-secretase gene is associated with HS. Since gamma-secretase cleaves intracellular Notch, the

defect of the Notch signaling pathway leads to the formation of follicular keratin-enriched epidermal cysts and negative regulation of Toll-like receptors, with a consequent excessive cornification in the pro-inflammatory environment.

Tobacco smoke is composed of many chemicals, some of which, along with nicotine, propagate the pathophysiological pathway described in HS. Along with nicotine, these chemicals activate keratinocytes via nicotinic acetylcholine (nAChRs) and aryl hydrocarbon receptors (AHRs), leading to acanthosis, infundibular epithelial hyperplasia, and excessive cornification (24). Nicotine also alters the host's defense by inducing the generation of pro-inflammatory cytokines by keratinocytes, chemotaxis, and Th17 cell induction (25). Moreover, nicotine elicits the proliferation of *Staphylococcus aureus* (26), and other tobacco smoke components enhance bacterial virulence by increasing cellular adhesion and inducing biofilm production (27,28). A study by Melnik *et al.* reported down-regulation of the Notch signaling pathway in active smokers, suggesting that cigarette smoke, which is prevalent in HS, may further suppress already deficient Notch signaling in HS (24).

Connecting the damaging effects of tobacco chemicals and nicotine with the pathomechanism that causes HS lesions seems to be one of the best explanations of a causal relationship between smoking and HS.

CONCLUSION

HS is a multifaceted skin disorder with a complex etiology involving genetic and environmental factors. An investigation into the etiology and nature of the disease presents an opportunity to identify and address modifiable risk factors that would potentially alter the incidence and the course of the disease. Smoking habits have been identified as one of the risk factors, as it has been observed that many patients with HS smoke. To scientifically prove the exact causal relationship between smoking and HS, large multicenter studies are needed instead of retrospective studies. Even though this relationship is likely to remain debatable, we strongly encourage patients with HS to quit smoking as evidence for damaging pathomechanism effects of nicotine, tobacco smoke, and its chemicals on skin and HS lesions is convincing. Thus, this review supports the hypothesis that environmental triggers, such as cigarette smoking, may result in the HS phenotype in a genetically susceptible individual.

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