Introduction

Acne vulgaris is gradually becoming recognized as an inflammatory disorder of the pilosebaceous unit. It is a common skin disease with a peak prevalence in teenage years but also occurs in girls pre-menarche and can continue to be a problem in women past adolescence. Although most epidemiological data in Western countries concern Caucasian skin types, acne is also a significant problem for Asian skin. In one large intercontinental, epidemiological study, the prevalence of clinical acne was reported to be similar between geographical zones, 24% in Caucasian, 30% in Asian and 23% in continental Indian women. However, acne type was found to vary between skin subtypes. Asian women were reported to have a higher prevalence of inflammatory acne than comedonal acne (20% vs 10%), compared to Caucasian women, for whom comedonal acne was more prevalent (14%) than inflammatory acne (10%).

In recent years, an increasing number of studies indicate a link between skin problems and exposure to airborne pollutants, such as particulate matter (PM), volatile organic compounds, ozone (O₃), nitrogen dioxide (NO₂) and sulfur dioxide (SO₂). As a recent example, NO₂ exposure has been linked to pigment spot formation on cheeks in both Caucasian and Asian women. Yet, few data are available today concerning the prevalence or exacerbation of acne symptoms and pollution exposure. Some anecdotal evidence emerged during an International Dermatology Conference in Beijing, where...
a survey of dermatologists revealed that 67% of responders agreed that acne prevalence increases with pollution (personal communication). However, little published evidence was found to support this relationship with the various types of airborne pollutants. One epidemiological study in China conducted in 2007 explored the prevalence of greasy skin in a metropolitan area and found that 25.6% of participants reported having greasy skin compared with a nonpolluted area. However, the authors did not evaluate acne signs as such. Two clinical studies conducted in two major cities known to have high pollution levels, Shanghai and Mexico City, found that skin quality changes with chronic exposure to ambient pollution. Skin quality changes were defined as reduced vitamin E and squalene levels, which are known signs of sebum oxidation. Also, similar to the Chinese study, the Mexican studies found raised sebum levels, but clinical signs of acne were not measured. Nevertheless, increased sebum is one of the known early, pathophysiological pillars of acne.

In 2014, an Eurasian board of experts published a state-of-the-art review of the current knowledge about the effects of common pollutants on the sensitive skin. The next step was to further investigate the link between airborne pollution and acne symptom exacerbation and to be able to propose appropriate measures to protect acne prone skin from further aggravation by pollution. A board of European and Asian scientists with expertise in dermatology gathered in 2015 to discuss the existing scientific evidence. This review summarizes the outcome of that meeting and subsequently initiated studies.

Methods

The Eurasian board of experts consisted of three European and four Asian scientists with expertise in dermatology, skin biology and environmental medicine. Each expert performed a literature review for research concerning acne prevalence and severity in association with pollution in their country, reviewed the current reports about acne symptom exacerbation and pollution as well as the current knowledge about the pathophysiology of acne and the mechanisms by which airborne pollution interacts with the skin. They were also asked to present their individual clinical experience treating acne in places with high atmospheric pollution.

A further literature review was performed using PubMed. Keyword combinations included air pollution + acne, ozone + acne, skin, PM$_{10}$, PM$_{2.5}$, particulate pollution, ozone, cutaneous disorders + air pollution, environmental stressors, atmospheric pollution, outdoor pollution and sebum. The most recent publications were chosen from key molecular and cellular studies, review articles, epidemiological studies, surveys and exploratory research in human subjects. The objective of the round table meeting was to evaluate the quantity and quality of the literature available. The experts were then to suggest whether further research was required to subsequently prepare a review paper and propose appropriate measures to protect acne prone skin in polluted environments. If further research was required, the board was to identify protocol outlines and workgroups to complete these research needs.

Results

Pathophysiology of acne as an inflammatory disease

The current understanding of the pathophysiology of acne is evolving. Acne is accepted to have a multifactorial etiology, based on three main observations: increased sebum production (under hormonal stimulation), abnormal keratinization of the pilosebaceous duct, and it is becoming increasingly evident that acne is driven by an inflammatory reaction to Propionibacterium acnes.

Two early events that occur when lesions appear are hyperseborrhea and follicular obstruction of the pilosebaceous unit. Several comprehensive review papers highlight recent molecular and cellular research that suggest with acne, the quality of sebum excreted on the skin surface changes. This alters the lipid composition and redox ratio on the skin surface. Within the follicular lumen, these qualitative changes in sebum production may result in an overall deficiency in linoleic acid, which disturbs the follicular barrier function. This situation creates a proinflammatory pattern with pro-inflammatory cytokine production and interleukin (IL)-1 upregulation, inducing follicular inflammation. It has been suggested that IL-1 production may also contribute to hyperkeratinization and the formation of the microcomedone. Also, immune cells (Th1) have been found in perifollicular regions of nonaffected skin in patients with acne, confirming the involvement of the innate immune system. These findings suggest that inflammation may have a critical role in acne development and progression.

One of the lipids produced by human sebaceous glands on the face and torso is squalene. This unsaturated fatty acid represents ~10%–15% of sebum and is readily oxidized by ozone, long ultraviolet (UV) rays and tobacco smoke. By-products produced from squalene peroxidation are known to be comedogenic and also demonstrate proinflammatory properties. High levels of squalene alter the redox balance in the skin leading to an excessive generation of reactive oxygen species (ROS) and a state of oxidative stress. Oxidative stress and nitrosative stress have been shown to...
occur in acne\textsuperscript{22} and may also be the trigger that sets off the acne cascade.\textsuperscript{23}

The proliferation of \textit{P. acnes} has long been considered the culprit of the acne cascade, yet this is no longer considered the case, because recent studies have found that \textit{P. acnes} predominates on both normal and disease-associated skins.\textsuperscript{24} However, a recent hypothesis suggests that the blocked pore makes the folliculopilosebaceous unit increasingly hypoxic. As \textit{P. acnes} is known to appreciate anaerobic microenvironments, such as the skin follicle, this situation is perfectly suitable for this usually commensal bacteria to grow. Proliferating \textit{P. acnes} is then recognized by follicular keratinocytes that start releasing inflammatory cytokines in response. The innate immune system is subsequently triggered when the duct ruptures, releasing \textit{P. acnes} into surrounding epidermal tissue, causing pustule formation and potentiating local inflammation.\textsuperscript{25} The innate immune system is thus recruited, helping to drive acne pathogenesis.\textsuperscript{14}

Nevertheless, increasing evidence demonstrates that some commensal organisms on human skin regulate the populations of pathogenic strains to maintain homeostasis. For example, \textit{Staphylococcus epidermis} mediates glycerol fermentation, hence inhibiting \textit{P. acnes} growth.\textsuperscript{26}

**Pollution as an inflammatory mediator**

Outdoor pollution is a heterogeneous mixture of chemicals and gases emitted into the atmosphere from natural and man-made sources. Those of major concern for the skin include both organic and inorganic compounds found in and on PM and gases such as ozone, nitrogen dioxide (NO\textsubscript{2}) and sulfur dioxide. Unsurprisingly, there are few data on visits for acne during peaks in pollution as many pollution and health studies are performed in accident and emergency departments, where acne patients do not usually present for exacerbation of their symptoms.

There is growing evidence that these pollutants exert their harmful effects by generating oxidative stress by means of ROS and inflammation. However, the exact mechanism is yet to be clarified. Various hypotheses have been proposed to explain how the detrimental effect of pollution starts. Vierkotter et al suggest PMs have an indirect effect by an outside–inside signaling pathway.\textsuperscript{8} O\textsubscript{3} has been shown to increase cytochrome p450 activation via the AhR.\textsuperscript{27} Recently, a direct action has been suggested by penetration through the stratum corneum.\textsuperscript{28} Once in the skin, the ROS cause a lipid peroxidation cascade, which stimulates the release of other proinflammatory mediators from keratinocytes and melanocytes, thus establishing a vicious inflammatory cycle, with infiltration of other potentiating cells such as neutrophils and other phagocytic cells.\textsuperscript{5} Polycyclic aromatic hydrocarbons, commonly found in air pollution, are known to also induce an inflammatory response.\textsuperscript{29–31} Finally, AhR activation (MMP, COX2, POMC, MITF) potentiates inflammation, which could theoretically increase acne.\textsuperscript{32}

This stress has been suggested to eventually overwhelm the skin’s natural defenses depleting its antioxidant capacity, such as vitamins C and E, contributing to a background inflammatory environment and disrupting the skin barrier function.\textsuperscript{33,34}

UV exposure has an additive effect with airborne pollutants and O\textsubscript{3}. UV irradiation is known to compromise the skin barrier and O\textsubscript{3} seems to heighten this phenomenon by disturbing stratum corneum lipid constituents that are known to be critical determinants of the barrier function. UV exposure and O\textsubscript{3} have also been found to have an additive effect on antioxidant depletion (vitamin E) and on lipid peroxidation levels, which could, in turn, lead to additional additive effects of these stressors.\textsuperscript{3} 35

**Acne treatments used in Asia**

Similar to most countries around the world, Asian dermatologists treat acne according to the Global Alliance or American Association of Dermatology guidelines. However, the board members remarked that some medical treatments disrupt skin barrier function. This being particularly problematic in Asian skin, which has been reported to have a higher prevalence and objective skin sensitivity compared with Caucasian skin.\textsuperscript{36,37} Also, there is an increasing awareness of antibiotic resistance due to many years of inappropriate topical antibiotic use and hence the need to find alternative solutions. Board members report a general trend toward using keratolytic (i.e., lipohydroxy acids, glycolic acid, salicylic acid)\textsuperscript{38} and anti-inflammatory ingredients (i.e., ketones, aldehydes, niacinamide) and sebum regulators, in combination with benzoyl peroxide (BPO) or retinoic acid.

In Thailand, it is difficult to implement the Global Alliance guidelines, so they developed their own recommendations. Patients are treated according to severity. They use photodynamic therapy (PDT) lasers to target comedones, but this has been found to be unsatisfactory as acne returns after treatment. In China, the board reports that traditional medicine remains popular for papulopustular acne and is used alongside the Global Alliance Guidelines. PDT (red and blue light) and glycolic acid are also used to treat comedones. In Korea, Chinese traditional medicine is also used, as well as essential oils, tea tree oil and ketone or aldehyde products with an anti-inflammatory activity.
Additional research
The first study to be performed following recommendations made by the Expert board was a large, epidemiological study in a dermatology hospital, Beijing, in 2016. Retrospective data were collected over a 2-year period and included 59,530 patients with acne. The authors found that increased ambient air concentrations of some of the most important traffic- and industry-related pollutants were associated with an increased number of outpatient visits for acne vulgaris. These associations were significant for NO2 in a single pollutant model, and NO2, PM10, and PM2.5 in two pollutant models, which reflect real exposure scenarios more closely (Wei et al, unpublished data, 2017). Also, a second, independent clinical study was performed by La Roche-Posay in Beijing, China, to investigate the relationship between exposure to the most frequent industry- and traffic-related air pollutants, that is, PM10, PM2.5, SO2, NO2, O3, and sebum level as well as the number of acne lesions (inflammatory and noninflammatory lesions). This 8-week study included 64 patients with acne who used the same skin care routine. Sebum rate was measured and acne lesions were counted each week. Air pollution data were obtained from the Beijing municipal environmental monitoring center. Increased ambient concentrations of PM10, PM2.5, and NO2 were associated with increased sebum secretion and a higher number of acne lesions. Higher ambient O3 concentrations were significantly associated with lower sebum rate and lower numbers of lesions (inflammatory and noninflammatory lesions) (unpublished data). Interestingly, both studies found that higher ambient SO2 concentrations were associated with fewer outpatient visits, lower sebum rates and lower numbers of both inflammatory and noninflammatory lesions. Together, these two studies indicate that exposure to air pollutants may aggravate acne vulgaris and inflammatory lesions. Together, these two studies indicate that exposure to air pollutants may aggravate acne vulgaris and inflammatory lesions. Combined these studies suggest that not all air pollutants have the same effect on acne skin.

Finally, L’Oréal Research and Innovation performed another study in two industrial areas in Asia to investigate the effect of ambient pollution on skin, including acne characteristics and severity. This study was retrospective in nature. It was observed that acne prevalence was significantly different between the two populations.

These results further support the pathophysiological links between acne prevalence and high ambient pollution levels.

Further research
Based on the literature searches and these three studies the authors suggest that more research is needed to better understand the link between acne and air pollution. In particular, the board suggested to further investigate the relationship between pollution exposure and squalene oxidation. Also, more research would be useful to understand the change in composition and quality of sebum with pollution.

Discussion and suggestions for appropriate protective measures
There is little data available to make strong recommendations for adjunctive skin care in acne management in polluted environments. Rocha et al recommends emollients and sunscreen in addition to drug treatment and suggests that patients be advised not to manipulate lesions.1 The natural skin barrier can be altered by using detergents that disrupt the skin lipid barrier, and induce the loss of antimicrobial peptides. This has been shown to allow S. epidermis to proliferate and attenuate the innate immune response.39 In light of the data available, the board supports the goal of dermocosmetic protection to reinforce skin barrier function. This prevents further provoking the inflammatory cycle and in turn associated problems such as aggravated disease severity and post-inflammatory pigmentation.

1. A skin care product dedicated to acne patients may provide a protective barrier from pollution, restore microbiome equilibrium to prevent overabundant bacteria (including P. acnes) colonization and control disease severity and post-inflammatory pigmentation, which is a concern in this population.

2. Some acne medication such as isotretinoin, topical retinoids and BPO dry the skin. Patients using these products should apply appropriate moisturizers as complimentary therapy to control skin dryness and restore skin barrier function.

3. Appropriate cleansers that do not further disturb the natural barrier function are suggested to eliminate pollution on the skin surface. Avoid using facial or body scrubs.

4. Certain acne medications are known to cause drug-induced phototoxicity. Sun protection should be encouraged: ensure the formulation has sufficient UVA and UVB protection, and is noncomedogenic and has a texture adapted to oily skin that provides moisture, while reducing sebum and facial shine.

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References
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