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Review Article

Urbanization, Environmental Pollution & Skin Aging

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Abstract: The skin aging process, which is induced by environmental factors, is named premature or extrinsic skin aging process and can be distinguished from the chronologically (intrinsic) skin aging process by characteristic skin aging signs. Although human skin acts as a biological shield against pro-oxidative chemicals and physical air pollutants, prolonged or repetitive exposure to high levels of these pollutants may have profound negative effects on the skin. Gender differences in toxicity have been reported for many substances. Children are known to be more vulnerable to the adverse health effects of air pollution. Environmental pollution by traffic is also associated with the occurrence of signs of extrinsic skin aging. Heavy metals such as cadmium, lead and mercury are common air pollutants that pose health hazards due to bioaccumulation. Ozone in the stratosphere has protective effects by filtering solar UV radiation; however, in the troposphere ozone has toxic implications for skin. Due to paucity of scientific evidence, there are no established guidelines currently available for protecting the skin against air pollution. Aside from reducing exposure, potential protection strategies should focus on repairing the skin barrier, replenishing antioxidant reserve, and reducing inflammation caused by air pollutants.

Keywords: Skin aging; particulate matter; Reactive Oxygen Species; collagen disruption; aryl-hydrocarbon receptor; photoaging.

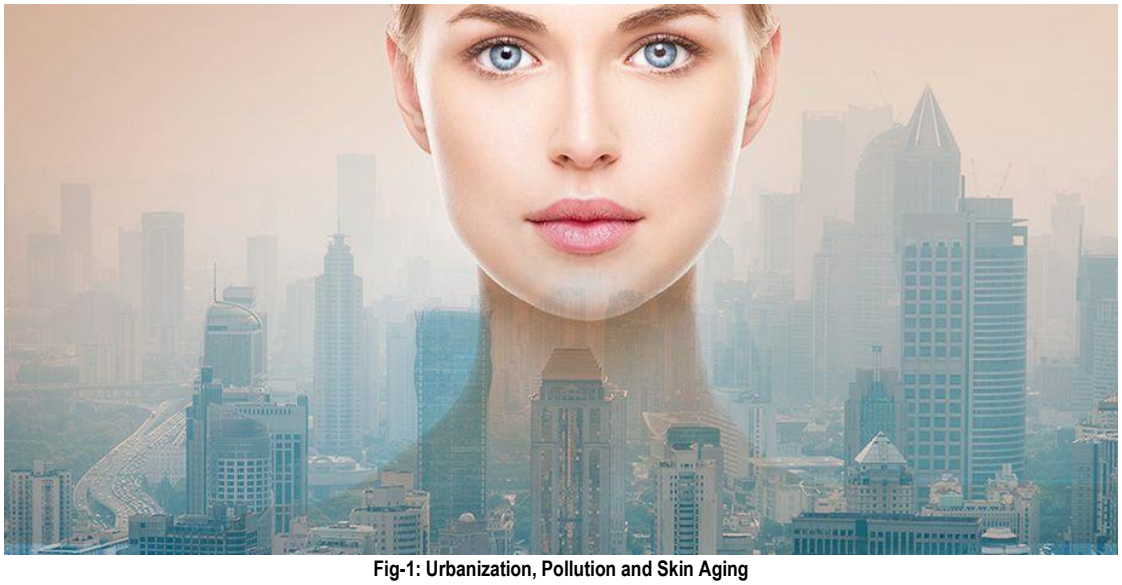

Fig-1: Urbanization, Pollution and Skin Aging

Skin is the body's largest organ, acts as a protective barrier that helps preserve our internal fluids and organs. Once this barrier is compromised, lipids and collagen (responsible for delivering hydration and plumpness to the skin) start to break down and the complexion suffers. Cue an increase in dry patches, spots and an overall lack of glow. This happens because highly unstable molecules, referred to as free radicals, derived from environmental pollutants. Urban people change their environment through their

consumption of food, energy, water, and land. And in turn, the polluted urban environment affects the health and quality of life of the urban population (Source: Hufton C. The facts on how pollution is impacting your skin. The Telegraph, 22 February 2019).

INTRODUCTION

Schraufnagel *et al.,* 2019 given estimation that about 500,000 lung cancer deaths and 1.6 million COPD deaths can be attributed to air pollution, but air pollution may also account for nearly 20% of all cardiovascular deaths and 21% of all stroke deaths [1]. Air pollution is prematurely ageing the faces of city dwellers by accelerating wrinkles and age spots, according to emerging scientific research [2]. Wang *et al*., 2018 and Liang et.al, 2019 reported that over 50% of the global population lives in urban areas since 2011- this is 3.9 billion, and by 2030, this number will rise to about 5 billion (more than 70%) [3, 4]. According to special reports of Health effect Institute, Boston published in 2018, exposure to fine particulate matter with a diameter of less than 2.5 μm (PM2.5) accounts for about 4.2 million premature deaths in 2016 [5]. PM2.5 rather than PM10 may be responsible for PM-induced toxicity. Pecorelli *et al*., 2019 pointed on ozone (O3), particulate matter (PM), and cigarette smoke, as some of the most noxious pollutants that city dwellers are exposed very day. Since the skin is the first line of defense against environmental insults, it is considered one of the main target organs for the harmful insults of air pollution [6]. NOx, CO, SO2, ozone, and volatile organic compounds (VOCs) are the most common gaseous pollutants. PM0.1 and other PMs are known to exert deleterious effects by acting as a "Trojan Horse" and carrying additional toxic compounds on their surface, including bacteria, carcinogens, acids, POPs, and metals. Sources of airborne mercury particles include combustion of coal and other fossil fuels. Urban communities and neighborhoods located near busy roads are exposed to high levels of TRP. Mancebo *et al*., 2015 stated that ambient air pollutants exert deleterious effects on the skin by generating free radicals, inducing cutaneous inflammatory cascades, activating AhR dependent mechanisms, and altering cutaneous microflora [7]. Furthermore, pollutant substances, mainly particulate matter (PM10, PM2.5), accelerate skin aging through specific activation of intracellular receptors called AhRs (aryl-hydrocarbon receptors), as depicted by Milani *et al*., 2019 [8]. Napolitano et.al, 2018 demonstrated that AhRs are involved in the pathophysiology of skin, including skin hyperpigmentation, photocarcinogenesis and skin inflammation [9]. Polycyclic aromatic hydrocarbons (PAHs), adsorbed on the surface of suspended PM, can trigger the arylhydrocarbon receptor (AhR) signaling pathway. The AhR might not only lead to an increased production of ROS, but also indirectly mediate transcriptional expression of genes, which are of known functional relevance for both wrinkle formation and pigment spot formation [10]. Yu *et al*., 2019 further added that indole-3-aldehyde (IAld), a tryptophan metabolite of the skin microbiota attenuates inflammation in patients with atopic dermatitis through the AhR [11]. Gutiérrez-Vázquez *et al*., 2018 stated that AhR is expressed by a number of immune cells, and thus, AhR signaling provides a molecular pathway that integrates the effects of the environment and metabolism on the immune response [12].

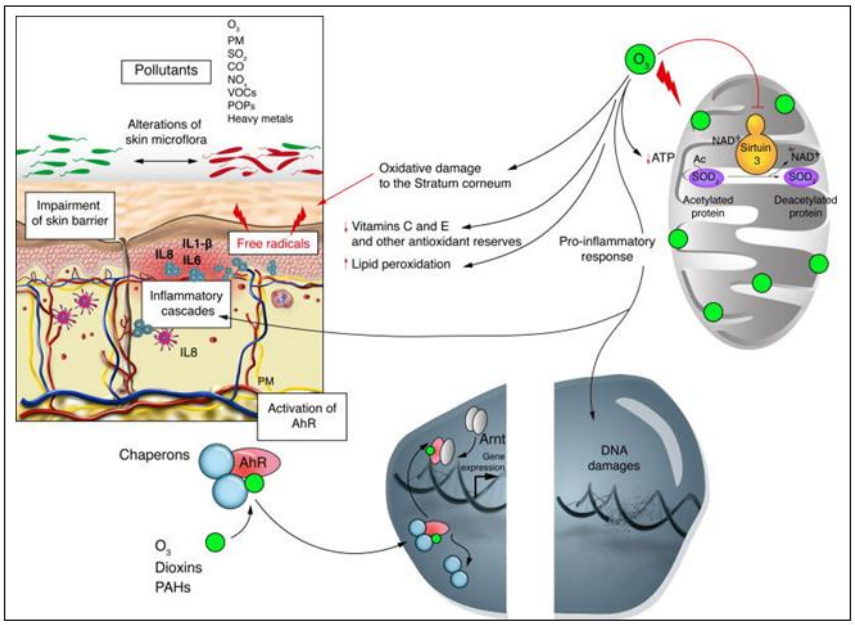

Fig-2: Schematic Diagram of Chronic Exposure of Pollutants on Skin [7]

Chronic exposure to ozone results in cumulative oxidative damage to the stratum corneum, ultimately generating free radical species. Furthermore, ozone depletes both enzymatic and non-enzymatic antioxidant reserves in the skin with notable effects on Vitamin C and E levels. In the mitochondria, ozone also depletes ATP and Sirtuin 3 levels, a protein involved in mitochondrial free radical scavenging. In addition to these effects, other pollutants are known to promote a pro-inflammatory environment in the skin resulting in increased levels of IL-1β, IL-6 and IL-8. These mediators activate granulocyte chemotaxis and phagocytosis. Ultimately, these combined processes result in direct and indirect toxicity to the skin. N.B. O3, ozone; PM, particulate matter; SO2, sulfur dioxide; CO, carbon monoxide; NOx, nitrogen oxides; VOCs, volatile organic compounds; POPs, persistent organic pollutants; IL - interleukin;

PAHs, polycyclic aromatic hydrocarbons; AhR, aryl hydrocarbon receptor; Arnt, AhR nuclear translocator; ATP, adenosine triphosphate; SOD2 - superoxide dismutase 2; NAD+, nicotinamide adenine dinucleotide.

An older study shows direct link between the chronic exposure to traffic-related particulate matter and the occurrence of prominent skin aging signs especially pigment spots, but also wrinkles in Caucasian women [13]. Schikowski *et al.*, 2019 further added that UVR is another important environmental factor which can cause skin aging and pigment spot formation. In a real exposure situation, human skin is exposed to both PM and UVR simultaneously [14]. Peng *et al*., 2017 added further suggested that the effects of air pollutants might be amplified in the presence of other air pollutants in conjunction with UVR [15]. According to Araviiskaia *et al*., 2019 pollutants reach the superficial and deeper skin layers by transcutaneous and systemic routes [16]. Fuks *et al*., 2019 says short-term exposure to ozone (O3) elicits an oxidative stress response in human, which leads to aberrant transcriptional expression of genes consistent with increased skin aging [17]. Park *et al*., 2018 demonstrated that PM10 contributes to skin inflammation and skin aging via impaired collagen synthesis [18]. Also, PM negatively affect the human skin and exacerbates preexisting skin disease [19, 20]. PM penetrates skin through hair follicles or sweat ducts, and across the stratum corneum (intracellularly or transcellularly) [18]. Also, Mohiuddin, 2019 reviewed that increased levels of 4 - hydroxy -2- nonenal (HNE) in the skin, in response to pollutants, likely accelerates skin aging and exacerbates existing skin inflammatory conditions [21]. Pecorelli *et al*., 2019 further stated that HNE is the main product of oxidative stress which derives from the oxidation of ω-6 polyunsaturated fatty acids (PUFAs). HNE is a highly reactive compound that can form adducts with cellular proteins and even DNA; it is also an efficient cell signaling molecule able to regulate mitogen-activated protein kinase pathways and the activity of redox-sensitive transcription factors such as Nrf2, AP1, and NFκB [6]. Hyun *et al.*, 2019 stated that atmospheric PM has harmful effects on humans through increasing the generation of reactive oxygen species (ROS), which have been reported to promote skin aging via the induction of matrix metalloproteinases (MMPs), which in turn can cause the degradation of collagen [22]. An indirect link between indoor air pollution and skin aging was established by Li *et al*., 2015, showing that the use of fossil fuels for cooking was associated with skin aging [20]. Bisphenol A (BPA) is an Endocrine disruptor compound (EDC), capable of interfering with hormone related pathways and cause adverse effects. Graziani *et al*., 2019 revealed that a total daily uptake via the skin corresponds to 9.3 µg per day [23]. Although it could account for as much as 51% of total exposure in occupationally exposed persons [24]. It may impart infertility, polycystic ovary syndrome, and endometriosis along with skin irritation and hypersensitivity. Everyone is exposed to BPA through skin, inhalation, and digestive system (produced for polycarbonate plastic, making it one of the highest volumes of chemicals produced worldwide) [25, 26]. Approximately 80% of all sicknesses and diseases can be attributed to inadequate water supply and sanitation worldwide [27]. According to New York Department of Health, chlorine is used to treat drinking water, it's also a toxic chemical. In large quantities strips the skin of its natural oils and causes it to dry and crack, which can lead to wrinkles [28]. Stefanovic *et al*., 2019 stated that specified exposomes of atopic dermatitis are humidity, ultraviolet radiation, diet, pollution, allergens, water hardness [29]. It is clinically manifested by itching and scratching, dry skin, patchy eczema especially on flexural locations, exudation, and skin thickening and discoloration [30]. It is well-documented that clinical manifestations of aging skin include loss of tone and elasticity, uneven skin tone, coarsened texture, enlarged pores, irregular pigmentation, and lines and wrinkles [31]. Acne scarring accentuates wrinkles later in life. It creates mini "facial crumple zones" throughout the face, particularly just below the corners of the mouth [32]. Melibary *et al*., 2019 reported that oxidative/nitrosative stress in the initiation of acne caused by the ozone, nitrogen dioxide (NO2) and sulfur dioxide as airborne outdoor pollutants as well as UV-rays, which plays an important role in the eruption [33]. UV exposure and O3 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. Thus, air pollution to worsens of acne symptoms [34]. Bocheva *et al.*, 2019 stated that air pollutants together with UVA, can act synergistically in initiation of skin cancers. In addition, PM induce skin aging through penetration of the epidermal layer of the skin and through adnexal structures [35]. It is well accepted in the scientific community that vitamin D compounds protect the skin against the hazardous effects of many skin aging-inducing agents, including UVR [36]. According to Mousavi et.al, 2019 air pollutants, especially ozone and PM can directly affect the cutaneous production of vitamin D [37]. Our antioxidant defenses such as vitamins C and E and selenium are obtained from the diet, and they are important for protection against UV-induced damage, beneficial for skin health and protection against aging-related changes. It has also been reported that excessive exposure to oxidant stress via pollutants or UV irradiation is associated with depleted vitamin C levels in the epidermal layer [38-41]. Whyand *et al*., 2018 further added that exposure to O3 results in dose dependent depletion of antioxidants vitamin C and E in the skin [7, 42]. Studies have shown a clear correlation between these factors and the appearance of melanosis and wrinkles. In addition to the UVR that contributes to cellular injury, visible radiation has an oxidative effect similar to that of infrared radiation via heat generation [43]. Addor *et al*., 2018 demonstrated significant changes in some of the mechanical properties of the stratum corneum by UV damage, reduce its cell cohesion and mechanical integrity; also affects the molecular structure of cell proteins and lipids [41]. This phenomenon is more marked in acne patients as the skin lipid film on the surface of the stratum corneum is altered through an increase in oxidized squalene and a decrease in linoleic acid [44]. Several experimental studies demonstrated the detoxifying activities of squalene against a wide range of chemicals such as arsenic and hexa-chloro-benzene [45]. There is evidence that metals in PM cause DNA, protein damage as well as apoptosis of skin cells through the mitochondria-regulated death pathway [47]. Exposure to metallic mercury higher levels for shorter periods of time can lead skin rashes [47]. Pb can affect Langerhans cells (antigen-presenting cells in the skin) in the production of interleukin 1β and expression of appropriate surface antigens (CD54, CD86, HLA-DR). It can also modulate the immune response of dendritic cells in the skin [48]. Face in particular is prone to effects of environment such as cold and hot weather, arid conditions, humidity, dust, pollution, and UVR [49]. Smoking causes premature aging which clinically manifests as deeper periorbital wrinkling. Premature facial skin aging in smokers, with a characteristic pattern of wrinkling and orange-purple skin discoloration, was

defined as smoker's face [50]. Smoker's face typically has lines or wrinkles radiating at the right angles from the upper and lower lips or corners of the eyes, deep lines on the cheeks, or numerous shallow lines on the cheeks and lower jaw [40]. An indirect link between indoor air pollution and skin aging was established by a study showing that the use of fossil fuels for cooking was associated with skin aging [18, 51, 52]. At the end, some of these environmental exposures are preventable by protecting the skin against sun exposure or by quitting smoking, but there are other environmental exposures like air pollution where up to now no protection is available. Newer therapeutic interventions should be based on the molecular mechanism by which air pollutants induce extrinsic skin aging.

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Abbreviations

Particulate Matter (PM); Aryl-Hydrocarbon Receptors (AhRs); 4 - Hydroxy -2- Nonenal (HNE); ω-6 Polyunsaturated Fatty Acids (PUFAs); reactive oxygen species (ROS); Matrix Metalloproteinases (MMPs); Polycyclic Aromatic Hydrocarbons (PAHs); Volatile Organic Compounds (VOCs); Traffic-Related Pollution (TRP); Indole-3-Aldehyde (IAld); Reactive Oxygen Species (ROS); Matrix Metalloproteinases (MMPs); Endocrine Disruptor Compound (EDC)

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