Smoking and Premature Skin Aging

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Intrinsic and extrinsic factors are involved in the skin aging process. Intrinsic aging is a slow, permanent degeneration that affects most of the body, with distinguishable characteristics such as wrinkling of the skin, cherry hemangiomas and seborrheic keratoses. Photoaging or photodamage is the most noticeable effect of extrinsic skin aging, caused by long-term solar UV light exposure. Photodamaged skin is illustrated by coarse wrinkles, dyspigmentation and telangiectasia, and is associated with malignant tumors.

Smoking is also an extrinsic factor in skin aging. The association of tobacco smoking and cardiovascular disease, lung cancer and chronic obstructive pulmonary disease is well-documented, and several studies have documented the adverse effect of tobacco smoking on the integumentary system.[1] In fact, today, multiple environmental factors are associated with facial aging; evidence suggests that smoking 20 cigarettes per day is equivalent in effect to almost 10 years of chronological aging. Therefore, lifestyle recommendations to stop or delay facial skin aging are also very useful in promoting public health.

Epidemiology of Skin Aging

The sallow complexion and markedly wrinkled skin of smokers was first noticed in 1856 during a large series of British insurance examinations. One year later, skin differences between smoking and nonsmoking British Army officers stationed in India were described. In 1965, the skin of 224 female cigarette smokers, ages 35-84, was evaluated and described as pale and thick, with a grayish hue and without local variations in pigmentation. However, because similar skin changes were noticed in nonsmoking women over the age of 70, these alterations were not fully interpreted.[2] In 1971, Daniell studied the severity of wrinkles in 1,104 smoking subjects. After adjusting for age and outdoor sun exposure, she noticed that premature wrinkling is an important sign of smoker's skin.[3]

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Subsequent studies also evaluated the correlation of smoking and premature skin aging. In 1981, one highlighted the characteristics of "smoking face," including: facial wrinkles, a prominence of underlying bony contours, atopic skin and a plethoric, slightly orange-purple or red complexion. The relationship between tobacco smoking and UV radiation exposure in skin aging was evaluated in a cross-sectional study. Using questionnaires, investigators assessed the sun exposure, pack-years of smoking history, and potential confounding variables of 83 subjects. A pack-year refers to the number of cigarette packs, containing 20 cigarettes each, smoked daily for one year's time.

In order to quantify facial wrinkles, the formula for the Daniell score was used: -1.24 + 0.05 × age + 0.015 × pack-year + 0.158 × sun exposure. Statistical analysis revealed that age [odds ratio (OR) = 7.5, at a 95% confidence interval (CI) = 1.72-19.87 and sun exposure (OR = 2.65, 95% CI = 1.0-7.0)] independently contributed to facial wrinkle formation. When sun exposure (> 2 hr/day) and heavy smoking (35 pack-years) occurred together, the risk of developing wrinkles was 11.4 times higher than that of non-smokers and those with less sun exposure (< 2 hr/day) and of the same age.[4]

In 2008, a Brazilian population including 110 men and 191 women (ages 25-86), of which 165 were nonsmokers and 136 were smokers or ex-smokers, was evaluated for connections between smoking and cutaneous aging. Investigators controlled variables including solar exposure, age, skin phototype, sex, sunscreen use, alcohol consumption, coffee consumption, sports participation, body mass index and history of relatives with precocious aging. Analysis of the data revealed that age, chronic sun exposure, skin phototype and tobacco load significantly related to the formation of facial wrinkles.[5] Heavy smokers, i.e., 40 packs/year, showed greater wrinkling at a ratio of 3.92/1.

Studies of twins provide an exceptional opportunity to minimize genetic variables. A cohort study, conducted with 65 pairs of twins, i.e., 130 individuals, investigated the probable causes of skin aging. Photodamage scores among twins, whether monozygotic or dizygotic, were highly correlated

($p = 0.92$). Further, using the Kruskal-Wallis test, differences in photodamage and other factors were associated with the quantity of cigarettes smoked ($p < 0.12$).[6]

Another study of twins uniquely evaluated pairs who had spent their first 20 years of life together. They also had the same type of job at the same latitude, resulting in well-matched levels of significant sun exposure. However, their smoking history was absolutely different. Here, Doshi et al. showed that one twin having a 52.5 pack-year smoking history showed significantly greater skin aging than their nonsmoking counterpart.[7]

Molecular Effects of Nicotine

Smoking-associated skin aging has multiple pathogeneses. At least 3,800 compounds are found in tobacco smoke, and although the effects of them all on connective tissue are not clear, those of nicotine have been investigated.[8] Nicotine is an agonist of acetylcholine. Acetylcholine is a neurotransmitter that is synthesized, secreted and degraded in keratinocytes. It has two different receptors, the nicotinic (nAChR) and the muscarinic (mAChR), both of which are present in skin.[9] In fact, a fresh, mature keratinocyte from human neonatal foreskin has about 35,400 binding sites for nAChR alone.

Nicotine acts specifically at the nAChR receptor, which is a 290-kDa protein consisting of a ring of five subunits. It enhances cell-to-cell adhesion, thus inhibiting keratinocyte migration. Smokers' poor wound healing can be explained by this mechanism. Moreover, nicotine is involved in keratinocyte differentiation by inducing calcium influx; in the epidermis, acetylcholine controls the terminal stage of keratinocyte differentiation through nicotinic channels, and this effect is mediated by the expression of different genes and calcium influx, which can result in squamatization. Nicotine can also enhance the apoptosis of keratinocytes using both cholinergic nicotinic agonists and muscarinic antagonists.[9]

Further, even just one cigarette can cause vasoconstriction and a decrease in blood flow. Black et al. showed that the acute exposure of human skin vasculature to nicotine affected endothelial functioning by amplifying norepinephrine-induced skin vasoconstriction and impairing endothelium-dependent skin vasorelaxation.[10] On the other hand, habitual smokers tend to have a longer vasorelaxation recovery phase, which may be evidence that microcirculation becomes accustomed to smoke.

Nicotine enhances cell-to-cell adhesion, thus inhibiting keratinocyte migration.

In relation, one underlying mechanism of skin aging is a decrease in skin tissue oxygen levels, and measurements of periorbital and periolar oxygen content before and after 30 min of smoking has shown a considerable increase in temperature and reduction in oxygen pressure without altering deoxy hemoglobin or the partial pressure of carbon dioxide.[11]

Cigarette smoke also contains the poisonous gases nitrogen oxide (NO) and carbon monoxide (CO). CO quickly enters the bloodstream, binds with hemoglobin and makes carboxyhemoglobin (CoHb), which decreases tissue oxygen levels. Exogenous NO increases arterial stiffness, in turn decreasing blood flow. Further, chemicals absorbed from cigarette smoke can become reactive oxygen species (ROS), and excessive amounts of ROS interfere with the enzymatic/gene pathway, causing multiple pathological disorders.[12]

Impact on Collagen

Studies have shown that tobacco smoke extract and other constituents dose-dependently induce matrix metalloproteinases (MMPs), which degrade collagen. MMPs trigger the aryl hydrocarbon receptor (AhR), a ligand-dependent transcription factor that mediates the toxicity of several environmental contaminants. The AhR molecule activates the transcription of genes to engage proteins in growth control, nuclear transcription and the regulation of extracellular matrix proteolysis, which ends in collagen degradation. MMP-1 in particular was shown to cause collagen and elastic fiber degradation in a study by Leshman et al., where higher levels of MMP-1 mRNA were identified in the dermal buttock connective tissue of smokers than nonsmokers.[13] In another in vivo study, tobacco smoke extract applied topically and intracutaneously to hairless male mice caused collagen damage, although intraperitoneal injection had no such effect.[14]

Besides degradation, tobacco extract can also directly impair collagen biosynthesis. Yin et al. demonstrated that the production of collagen precursors procollagen type I and III is significantly decreased in supernatants of cultured fibroblasts treated with tobacco extract. This experiment also proved that the balance between metalloproteinase and tissue inhibitors of metalloproteinase was disturbed in favor of MMPs.[15]

Transforming growth factor (TGF-β1) is a multifunctional cytokine that regulates cell proliferation, differentiation, tissue remodeling and repair. In the epidermis, TGF-β1 acts as a growth inhibitor by maintaining tissue homeostasis; however, in the dermis, it works like a potent growth factor by inducing the synthesis of extracellular matrix proteins. This molecule initiates a signaling pathway through a heterometric complex of type I/II TGF-β receptors, which finally activates signal transduction pathway. Yin et al. also showed that tobacco smoke extract induces the non-functional form of TGF-β in supernatants of cultured skin fibroblasts. The lack of biological response to this non-functional form

in turn causes the down-regulation of the TGF-β receptor, which decreases extracellular matrix protein synthesis. The researchers suggested this could be evidence that tobacco smoke impairs collagen production.[8]

Conclusion

Cutaneous aging is a continuous process. Intrinsic aging is inevitable due to physiological changes in all body organs.[5] Among various environmental or extrinsic factors, tobacco smoking has been studied by several authors and their investigations support the strong association of smoking with premature skin aging, development of wrinkles, and marked alterations of skin structures and composition of the epidermis.

Tobacco's role in premature skin aging provides leverage to encourage smokers to quit or reduce smoking for the sake of appearance—in addition for the sake of their general health. Based on ongoing research and the literature presented, dermatologists can now assist in smoking prevention and cessation campaigns by counseling patients and providing them with information about the increased risk of facial wrinkling associated with cigarette smoking.

References

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1. L Misery, Nicotine effects on skin: Are they positive or negative? *Exper Derm* 13(11) 665-70 (2004)
2. M Ippen and H Ippen, Approaches to a prophylaxis of skin aging, *J Soc Cosmet Chem* 16 305-8 (1965)
3. HW Daniell, Smoker's wrinkles: A study in the epidemiology of crow's feet, *Ann Intern Med* 75(6) 873–880 (Dec 1971)
4. L Yin, A Morita and T Tsuji, Skin aging induced by ultraviolet exposure and tobacco smoking: Evidence from epidemiological and molecular studies, *Photoderm, Photoimmunol and Photomed* 17(4) 178–83 (2001)
5. APP Raduan, RR Luiz and M Manela-Azulay, Association between smoking and cutaneous aging in a Brazilian population, *J Euro Acad Derm and Venereology* 22(11) 1312–8 (2008)
6. KJ Martires, P Fu, AM Polster, KD Cooper and ED Baron, Factors that affect skin aging: A cohort-based survey on twins, *Arch Derm* 145(12) 1375–9 (2009)
7. DN Doshi, KK Hanneman and KD Cooper, Smoking and skin aging in identical twins, *Arch Derm* 143(12) 1543–6 (2007)
8. L Yin, A Morita and T Tsuji, Tobacco smoke extract induces age-related changes due to modulation of TGF-beta, *Exper Derm* 12 suppl 2, 51-6 (2003)
9. *Ibid Ref 1*
10. CE Black et al, Effect of nicotine on vasoconstrictor and vasodilator responses in human skin vasculature, *Amer J Physiology,* 281(4) R1097–104 (2001)
11. G-B Fan, P-L Wu and X-M Wang, Changes of oxygen content in facial skin before and after cigarette smoking, *Skin Res and Tech* (2011)
12. *Ibid Ref 11*
13. A Morita, K Torii, A Maeda and Y Yamaguchi, Molecular basis of tobacco smoke-induced premature skin aging, *J Invest Derm* 14(1) 53–5 (2009)
14. H Tanaka et al, Tobacco smoke extract induces premature skin aging in mouse, *J Derm Sci* 6(1) 69–71 (2007)
15. *Ibid Ref 13*

Additional reading: M Rahvar, Smoking and skin aging, in: Textbook of Cosmetics Dermatology, 3rd edn, *AO Barel, M Paye and HI Maibach, eds, Informa Healthcare, New York (2012)* C&T