A Holistic Approach to Antiaging as an Adjunct to Antiaging Procedures: A Review of the Literature

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BACKGROUND Aging is a multifactorial process and depends on both intrinsic and extrinsic factors. Procedural options for diminishing signs of intrinsic aging and cosmetic rejuvenation have expanded dramatically. However, less attention is paid to counseling patients on options for mitigating extrinsic factors related to aging.

OBJECTIVE The objective of this study was to review changes that occur with intrinsic and extrinsic aging, and provide evidence-based holistic counseling recommendations that can be used synergistically with aesthetic procedures to maximize antiaging interventions.

MATERIALS AND METHODS A PubMed search was conducted for articles on intrinsic and extrinsic aging as it relates to skin, fat, muscle, and bone. Key clinical trials and studies on the effect of diet, hormones, exercise, sleep, stress, dental hygiene, smoking, pollution, and oxidative stress on the aging process are reviewed, and treatment recommendations are summarized based on available evidence.

RESULTS Conventional cosmetic procedures and cosmeceuticals work together with nutritious diet, exercise, dental hygiene, hormonal balance, stress reduction, smoking and pollution avoidance, and healthy sleep patterns for a better effect on antiaging.

CONCLUSION A combination approach of multiple nonsurgical modalities along with healthy lifestyle recommendations to minimize intrinsic and extrinsic aging factors allows cosmetic practitioners to target multiple facets of aging concurrently and maximize the aesthetic interventions cosmetic dermatologists/practitioners provide.

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It is generally accepted that aging has 2 principal determinants: the intrinsic disposition (genetic make-up, somatic capacity, and composition) delineating what is maximally possible, and extrinsic factors (nutrition, exercise, hormones, dental hygiene, stress, and environmental influences) determining how the preset frame of opportunity is exploited in the course of the individual aging trajectory.

All human skin is subjected to intrinsic aging, whereas extrinsic aging is restricted to sites exposed to environmental factors such as sunlight and visible and infrared light (IR).[1] Procedural options available to patients for diminishing signs of intrinsic aging have expanded dramatically, and include neuromodulators, fillers, sclerotherapy, chemical peels, liposculpture, lasers, and light or energy devices, and continues to grow. However, other than sun protection counseling, less attention is paid to options for mitigating the affects other extrinsic factors have on aging. Ultimately, aging is an oxidative process, which results in receptor-initiated signaling, mitochondrial damage, protein oxidation, and telomere-based DNA damage responses at the cellular level,[2] beyond just the keratinocytes and fibroblasts, but also osteocytes, skeletal muscle, smooth muscle, and adipocytes. As patients view their cosmetic dermatologist as their "antiaging" physician, perhaps the aesthetic consultation

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should also include a more holistic approach on antiaging. This review will focus on the changes that occur with both intrinsic and extrinsic aging, and provide evidence-based lifestyle counseling recommendations to optimize antiaging interventions and more comprehensively help the patients antiage.

Intrinsic Aging/Factors

Bone Changes

Bone is a living tissue that is constantly remodeling, and this physiologic process maintains bone integrity and mineral homeostasis.[3] Recent studies have demonstrated that oxidative stress induced by reactive oxygen species (ROS), which increase with aging, can adversely affect bone homeostasis.[4–7] As a result of the oxidative stress, bone formation by osteoblasts is reduced, whereas osteoclast differentiation and activities and subsequent bone resorption are enhanced directly or indirectly through an increased receptor activator of nuclear factor-kappa β ligand (RANKL) production.[8]

With respect to facial bone structure, a reduced number of osteons and osteocytes are seen in the facial bone of subjects older than 35 years when compared with those younger than 35 years. This adds to the lack of craniofacial skeletal support to overlying soft tissue in both men and women.[9] On the midface, resorption and posterior remodeling of maxillary bone further accentuates the nasolabial folds and aids in displacing the malar fat pad inferiorly.[10,11] Alveolar ridge and mandibular resorption, up to 3 to 6 mm by the age of 60, as a result of tooth loss and aging may also promote perioral and melolabial volume loss.[12,13] Widening of the orbital socket results in the development of a "tear trough" deformity and loss of 3-dimensionality of the cheeks. The combination of soft tissue and skeletal changes thereby contribute to the "inverted triangle" appearance of the aging face.

Muscle Changes

There is evidence that ROS play an important role in the human muscle aging process.[14] During aging, there is an accumulation of oxidative damage in muscle and an inability to activate the cytoprotective proteins such as heat shock proteins and antioxidant defense enzymes such as superoxide dismutase enzymes.[15,16]

With respect to facial musculature, mimetic muscles do not have significant side-to-side difference. In contrast, right-handed individuals prefer to chew on the right side, and vice versa.[17] This can explain the significant left-right side differences of the temporalis muscle. The mimetic musculature does show gender differences with the mentalis, depressor anguli oris, and depressor labii inferioris being smaller in women, but the zygomaticus and frontalis muscles being larger in men.[18] Nevertheless, with age, facial mimetic muscles no longer have the cranial support (secondary to bony loss) that they once had. As they try to maintain a resting tone, repetitive facial movement gives rise to wrinkles that once were only noticeable at movement and soon become noticeable at rest.

Fat Changes

Recent data have linked accelerated fat aging and oxidative stress in adipocytes.[19] An in vitro study subjected adipocytes to oxidative stress and senescence induction by a variety of means for 2 weeks and found that compared with untreated cells, both ROS generation and DNA damage were significantly higher in cells subjected to oxidative stress and senescence. Adipocytes subjected to oxidative stress also showed shortened telomeres.[19]

Studies by Rohrich and Pessa elucidated a framework of superficial and deep facial fat compartments discretely partitioned into multiple, independent units by facial barriers.[20–22]

Facial fat loss in temporal, malar, mandibular, and preauricular areas and interior fatty prominence in the jowls, nasolabial folds, and submental locations compound the aging appearance.[23] A study comparing midfacial fat compartments in cadavers 54 to 75 years of age versus those 75 to 104 years of age did find a smaller subcutaneous extension of the buccal fat pad in the older group compared with the younger group, and deflation of this compartment may lead to the lack of support for the medial and middle cheek fat, as well as suborbicularis oculi fat, aggravating the descent of these compartments.[24]

Skin and Hair Changes

Skin's intrinsic deterioration is related to a progressive, age-related decline in antioxidant capacity coupled with an increased production of ROS from oxidative metabolism in cells of the skin.[25,26] Multiple biochemical pathways that are triggered by ROS overload result in suppression of transforming growth factor-β receptor II (TGF-β-R2),[27] overexpression of matrix metalloproteinases (MMPs),[28] and increased inflammation through the nuclear factor kappa β pathway.[29] This results in breakdown of the collagen and elastin network in the dermis manifesting clinically as xerosis, loss of elasticity, atrophy, dyschromia, and rhytides.

Intrinsic hair aging is caused by hair follicle stem cells (HFSCs) that accumulate DNA damage over time and undergo proteolysis of type XVII collagen (COL17A/BP180).[30] As a result, HFSCs terminally differentiate and leave behind miniaturized hair follicles, as seen in androgenetic alopecia (AGA). Interestingly, thinning hair was seen in COL17A1-deficient mice, whereas hair maintenance was seen in COL17A1 overexpressing mice. Miniaturized follicles in human samples also showed reduced COL17A1.

Extrinsic Aging/Factors

Sun Exposure

Extrinsic factors augment the intrinsic deterioration, and of all the factors affecting the tissues, cumulative sun exposure is the most important. Cutaneous signs of chronic sun exposure include rhytides, lentigines, telangiectasias, keratoses, loss of elasticity, dyschromia, and poikiloderma of the neck and chest with elastosis. Based on the recent literature, the damaging effects on human skin are a combination of ultraviolet radiation (UVR), visible light, IR, and heat.[2,31–33] Interestingly, the common feature that links skin damage to these different solar wavelengths is the enhanced production of reactive molecule species, and thereby increased oxidative stress.[34] Furthermore, physical changes in hair fiber properties (increase in fiber porosity, loss of mechanical strength, and an increase in surface roughness) are also induced by oxygen free radicals created by UVR.[35,36]

Although UV irradiation cannot penetrate into subcutaneous fat layer, acute and chronic UV exposure to the skin can lead to alteration of adipokines in subcutaneous fat tissues.[37,38] A study found that the expressions of adiponectin, leptin, and their receptors were significantly decreased in subcutaneous fat of sun-exposed forearm skin, in comparison with that of sun-protected buttock skin of the same elderly individuals.[38] In addition, this decrease in adipokines was noted to further cause exacerbation of photoaging by stimulating MMP-1 expression and inhibiting procollagen synthesis. These findings highlight that cell signaling does not occur in a vacuum and that there is cross talk and signaling between epidermal, dermal, and subcutaneous adipocytes.

Recommendation

Sun protection of the skin is paramount and should also apply to hair. As mentioned, skin damage is due to the different solar wavelengths (UVR, IR, and heat), so it is important to apply a cosmetically pleasing sunblock that not only has physical blocker properties (i.e. titanium or zinc oxide) that protects against both UVA and UVB, but also has a blend of antioxidants that provides IR and heat protection while minimizing inflammation and promoting skin repair.[39] Furthermore, American Academy of Dermatology (AAD) recommends that everyone use a sunscreen that has sun protective factor 30 or higher and is water resistant. As per AAD, sunscreen should be reapplied approximately every 2 hours, or after swimming or sweating. In addition to wearing sunscreen, AAD recommends taking the following steps to protect your skin: seek shade (especially between 10 AM and 2 PM), wear sun protective clothing (long-sleeved shirts, pants, wide-brimmed hat, and sunglasses), and use extra caution near water, snow, and sand (as they reflect the damaging rays of the sun).[40]

Pollution

Air pollution is another environmental factor related to premature skin aging. A recent epidemiological study comparing women living in urban and rural environments discovered a direct link between airborne particulate matter (PM) exposure and the occurrence of prominent skin aging signs especially

pigment spots (20% increase of spots on forehead and cheeks), but also wrinkles.[41] Ambient PM exerts its detrimental effects through the generation of oxidative stress[42] and mitochondrial damage.[43] As oxidative stress also plays a role in hair aging,[35] it would be reasonable to postulate that pollution can also negatively affect hair aging.

Research has also linked pollution as a contributing factor to bone loss. A recent study combining data from 2 national databases evaluated the risk of osteoporosis in Taiwanese residents exposed to air pollution, and concluded that exposure to the highest level of air pollutants might increase 39% to 89% risk of osteoporosis.[44]

Recommendation

It is recommended that patients are educated regarding the need for better protection from air pollution. Sunscreens are not effective for pollution, so the best defense for skin against air pollution is a routine of cleansing to remove PM that can attach to the skin, combination of topical (vitamins C and E, and ferulic acid) and systemic (diet with high intake of fruits such as blueberries, vegetables, nuts, olive oil, fish, whole grains, and legumes) antioxidants to counteract the oxidative stress produced by PM, and barrier repair with moisturizers creating a protective field against PM. Also, use scarf or hats to protect hair from direct damage by pollution. Consider avoiding air pollutants in general to decrease risk of osteoporosis.

Smoking

Smoking is another independent skin aging–inducing environmental factor, and the effect of sun exposure and smoking is addictive.[45] A number of studies have confirmed association between smoking and premature wrinkling,[46,47] In a study of 79 pairs of twins, in which only one twin smokes or where one twin smoked at least 5 years longer than his or her counterpart, it was found that smoking twins compared with their nonsmoking counterparts had worse scores for upper eyelid skin redundancy, lower lid bags, malar bags, nasolabial folds, upper lip wrinkles, lower lip vermillion wrinkles, and jowls.[48] In vitro studies have demonstrated that smoking leads to a decrease of collagen I and III as well as an upregulation of the MMP-1 and MMP-3 messenger RNA, which are involved in degradation of collagen, elastic fibers, and proteoglycans.[45,49] Relationship between smoking, baldness in men, and premature gray hair has also been described in the literature.[50] A study of Asian men 40 years or older showed statistically significant positive associations in a dose–response pattern between severity of AGA and smoking status, current cigarette smoking of ≥20 cigarettes per day, and smoking intensity.[51] The mechanisms by which smoking causes hair loss are multifactorial, including oxidative stress.[52]

As per recent meta-analysis studies,[53,54] smoking had no material effect on bone mineral density (BMD, refers to the amount of minerals [mostly calcium and phosphorous] contained in a certain volume of bone, and is used to identify osteoporosis and fracture risk) in premenopausal women; however, in postmenopausal women, bone loss was greater in smokers—an additional 2% for every 10-year increase in age, with a difference of 6% at age 80. In current smokers relative to nonsmokers, the risk of hip fracture was estimated to be 17% greater at age 60, 41% greater at 70, 71% greater at 80, 108% greater at 90.[53] The data in men are limited but suggest a similar proportionate effect in smokers. Smoking history has also been associated with a significantly increased risk of fracture compared with individuals without a smoking history, but the risk was lower than for current smokers.[54]

Recommendation

It is recommended to ask patients about smoking habits and advise them about benefits of smoking cessation—healthier skin and protection from hair loss and low BMD and to encourage patients to quit smoking and refer motivated patients to primary care provider to consider behavioral and social support programs (individual, group, and telephone counseling) and pharmacotherapy (nicotine patch, bupropion, varenicline). Counseling and medication are effective when used by themselves; however, the combination of counseling and medication is more effective than either alone.[55]

Diet

The role of diet in aging skin is highly controversial with limited available scientific data. Even worse, nutrition education is in very short supply during and after medical school graduation.[56]

An important aspect of a healthy diet is following a low-glycemic diet, which is low in refined carbohydrates and processed foods and high in vegetables and lean protein, helping to keep the blood sugar levels stable. Ingestion of sugar promotes cross-linking of collagen fibers through a process known as glycation, leading to the production of tissue-destroying advanced glycation end products (AGEs).[57] Protein glycation and AGE formation are associated with increased free radicals in skin collagen, which accelerates skin aging.[58] Preformed AGEs, such as those produced by heat, are another source of increasing the AGE burden of skin aging. Grilling, frying, deep-fat frying, or roasting produce high levels of AGEs compared with cooking processes involving water.[59] Given that the gluten-free diet is low in high-temperature–processed foods and in flour-based items, which are generally high in AGEs,[60] this diet might have beneficial effects in improving skin health and aging. However, prospective studies need to be performed to confirm this association.

Another promising strategy for enhancing skin protection from oxidative stress is to support the endogenous antioxidant system with diet rich in antioxidants. A study looked at skin wrinkling in a sun-exposed site in older people of various ethnic backgrounds (Swedish subjects living in Sweden, Greek subjects living in rural Greece, Anglo-Celtic Australian elderly living in Melbourne) and concluded that persons who consumed a high intake of vegetables, olive oil, and legumes but a lower intake of milk and milk products, butter, margarine, and sugar products had less wrinkling.[61] One hypothesis is that the former food group may have partly contributed to reduced skin wrinkling because of high content of antioxidant vitamins and phytochemicals.

Some diets have been better studied than others. One of the most popular diets—the Mediterranean diet—that emphasizes the consumption of fruits, vegetables, fish, nuts, legumes, whole grains, and intake of monounsaturated fat, as well as avoidance of red and processed meats, has been associated with low mortality and morbidity from some chronic diseases.[62,63] Mediterranean diet is also helpful for healthy skin as it has been linked to reduced oxidative stress. In a well-controlled study of twins, higher adherence to Mediterranean diet was associated with higher ratio of reduced to oxidized glutathione in the plasma, which translates into lower oxidative stress.[64] Furthermore, increased adherence to the Mediterranean diet has been shown to have protective associations with BMD,[65] as well as with a lower risk for hip fractures.[66]

Last, another study examining associations between nutrient intakes and skin aging in 4,025 American women (40–74 years) using a 24-hour recall found that higher intakes of vitamin C and linoleic acid from food sources such as fruit, vegetables, and nuts were associated with a lower prevalence of a wrinkled appearance, senile dryness, and skin atrophy, whereas higher intakes of fats and carbohydrates were associated with a higher likelihood of features of skin aging.[67]

Recommendation

Combination of a Mediterranean diet and a low glycemic diet, along with food sources containing vitamin C and linoleic acid (i.e. a diet with high intake of fruits, vegetables, nuts, olive oil, fish, whole grains, lean protein, legumes, and monounsaturated fat but a lower intake of refined carbohydrates, sugar products, processed foods, butter, saturated fat, fried food, red and processed meat), can promote healthier skin and may have a protective effect on BMD.

Exercise

Like diet, there is very limited scientific data available on the effect of exercise on skin aging. However, recent research by Tarnopolsky and his colleagues tested the effects of exercise on the skin of human volunteers aged between 20 and 86.[68] The study had 2 groups of individuals—sedentary (exercising for less than an hour per week) and active (doing at least 4 hours of

high-intensity aerobic exercise each week). A biopsy taken from each volunteer's sun-protected buttock skin demonstrated that those who exercised frequently had significantly thinner, healthier stratum corneum and increased reticular dermis collagen content when compared with those who were sedentary. The skins of the exercisers (even those older than 65 years) were much closer in composition to those of 20 and 30 years olds.[68] The authors identified exercise-induced interleukin-15 as a hormone that mediates the health of skin tissue.

Furthermore, a meta-analysis study which looked at the effect of physical activity on the bone mass of healthy postmenopausal women older than 50 years found a significant protective effect of physical activity (walking, running, physical conditioning, and aerobics) on BMD at the L2-4 level of the lumbar column; however, no effect was noted on forearm and femoral bone mass.[69] Similarly, results of a recent study that compared muscle structure and function in (1) male participants belonging to a group of well-trained seniors (average age of 70 years) who exercised regularly in their previous 30 years of age and (2) age-matched healthy sedentary seniors with (3) active young men (average age of 27 years) indicated that lifelong physical exercise preserves muscle structure and function in well-trained elderly men such that it is comparable with active men 4 decades younger than to that of age-matched sedentaries.[70]

Recommendation
It is recommended to encourage at least 4 hours of moderate or high-intensity physical exercise each week to promote healthier skin and to consider cycling, walking, running, physical conditioning, and aerobics as they have been shown to have a protective effect on BMD as well as muscle structure and function.

Sleep

Short sleep duration has become increasingly common in modern society. Recent data suggest that significant differences exist in skin aging and function between individuals who have healthy sleep patterns versus those who do not. Poor-quality sleepers (Pittsburg Sleep Quality Index [PSQI] >5, sleep duration ≤5 hours) had significantly higher intrinsic aging scores than good quality sleepers (PSQI of ≤5 and sleep duration of 7–9 hours). Poor sleepers also had diminished skin barrier function (higher transepidermal water loss) and lower satisfaction with appearance (self-perception of attractiveness).[71,72] There are indications in the literature that increased oxidative stress plays a key role in mediating the negative effects of sleep disturbances.[73]

A recent study of 602 Chinese women aged 18 to 80 years showed that when compared with those who slept 8 hours, individuals who slept 6 hours or less had significant lower total and regional BMD.[74] These significant associations between BMD and sleep duration were only observed in 45 years or older group. A cross-sectional analysis of 1,196 older (>60 years of age) subjects supports the hypothesis of a link between sleep and muscle mass.[75] The study found that bad sleep quality and low sleep efficiency in older people are associated with reduction in muscle mass and function. Age-related sleep problems potentially interfere intracellularly by inhibiting anabolic hormone cascades and enhancing catabolic pathways in the skeletal muscle.[76]

Recommendation
It is recommended to encourage patients to get a good-quality sleep of 8 hours at night to improve skin barrier function, satisfaction with appearance, BMD, and muscle mass and function.

Dental Hygiene and Care

Because the facial skeleton changes profoundly with aging as a consequence of significant resorption of the bones of dental origin in particular, it should be of interest to cosmetic dermatologists to educate their patients on dental hygiene and care. The teeth support the lower third of the face, and over time that support begins to collapse as there is loss of teeth which is frequently associated with periodontal disease in older adults.[77] When there is teeth loss, the demand for support in the bone surrounding the teeth is decreased, leading to a resorption of bone in those nonactive areas. This process is more pronounced in the upper

jaw than in the lower jaw, and the presence of less bony tissue in the upper jaw decreases the height of the face and causes the lower jaw to appear more prominent.[78] In this way, tooth loss has a significant effect on underlying skeletal proportions of the face, and along with fat loss leads to the formation of wrinkles and hollow cheeks, and affects the muscles of the lower face, which must compensate for the absence of teeth.[79] The total face height ratio remains stable throughout adulthood among individuals who have relatively intact dentitions.[80]

Recommendation

Good oral hygiene and regular dental examination are key to preventing periodontal disease that can result in tooth loss and subsequent bone resorption. The American Dental Association (ADA) recommends brushing teeth twice a day with a soft-bristled brush and flossing at least once a day to help remove plaque from the areas between your teeth where your toothbrush cannot reach. Last, ADA encourages patients regarding regular dental visits, at intervals determined by their dentist to accommodate for their current oral health status and health history.[81]

Stress

Chronic psychological stress stimulates the autonomic nervous system, renin–angiotensin system, and the hypothalamic–pituitary–adrenal axis, and prolonged activation of these pathways can result in chronic immune dysfunction, increased production of ROS, and DNA damage, which are known to contribute to the aging of skin, and other tissues.[82,83] A recent cross-sectional study, aimed to identify risk factors for premature hair graying (PHG) in young Turkish adults, found that perceived stress scale score (marker of emotional stress) was significantly higher in the PHG group than in participants without PHG.[84] Stress has also been implicated as one of the causal factors involved in hair loss (AGA, telogen effluvium, and alopecia areata).[85]

Chronic psychological stress is also associated with bone loss as it results in hyperactivity of sympathetic nervous system, glucocorticoid (GC), and interleukin-6, together with suppression of gonadal hormones and growth hormone, leading to decreased bone formation and to bone loss.[86] Furthermore, GCs are believed to promote muscle atrophy by means of motivating ubiquitin proteasome system and can repress muscle protein synthesis by inhibition of PI3-kinase/Akt pathway.[87]

Recommendation

As per the National Center for Complementary and Integrative Health (Federal Government's lead agency for scientific research on complementary and integrative health approaches), mind and body approaches may help in stress management. Some examples of these approaches are as follows: mindfulness meditation, yoga, tai chi, qi gong, progressive relaxation, guided imagery, biofeedback, self-hypnosis, and deep breathing exercises.[88]

Hormones

For women, decrease in estrogen during menopause has been noted to increase skin dryness, and decrease skin elasticity, dermal thickness, and skin collagen content.[89–92] Experimental data have shown that the presence of estrogen may protect skin cells against oxidative damage and that the dramatic lowering of estrogen levels during menopause could render skin more susceptible to oxidative damage.[93] Although several trials have shown that hormone replacement therapy (HRT) and estradiol-based creams improve skin quality (skin elasticity and hydration,[94] increased collagen content with improved texture and firmness,[95] fewer wrinkles[96]), however, much of the evidence is controversial and there are some studies that did not show remarkable improvements.[97]

Decline in female estrogen levels with age also increases the amount of bone resorption.[98–100] Furthermore, a low dietary intake of vitamin D and calcium hastens bone loss and osteoporosis.[101] A recent study showed that the use of vitamin D and calcium supplements affects periodontal disease status. Compared with subjects who did not take vitamin D and calcium supplementation, supplement takers had shallower probing depths, fewer bleeding sites, lower gingival index values, fewer

furcation involvements, less attachment loss, and less alveolar crest height loss.[102]

Recommendation

Given the increased risk of breast cancer, stroke, and thromboembolic disease in HRT users, and increased risk of endometrial cancer with unopposed estrogen use, the risk-to-benefit ratio of this therapy needs to be carefully evaluated by physicians and their patients.

As per National Osteoporosis Foundation recommendations, women (50 years or younger) and men (70 years or younger) should consume a total of 1,000 mg of calcium daily from diet and supplements, whereas women (51 years or older) and men (71 years or older) should consume 1,200 mg. As for vitamin D, men and women younger than 50 years should consume at least 400 to 800 international units (IU) daily, and those who are 50 years or older should consume at least 800 to 1,000 IU (the safe upper limit is 4,000 IU daily for most adults).[103]

Conclusion

Given that facial aging involves the interplay of a number of concomitant factors, it is not surprising that patients would require concurrent treatment with multiple different modalities to optimize their antiaging regimens. Patients consider their cosmetic dermatologists as their "antiaging" doctors, and as such, cosmetic dermatologists/practitioners should emphasize the need for a healthier lifestyle including nutritious diet, exercise, dental hygiene, hormonal balance, stress reduction, smoking and pollution avoidance, and healthy sleep patterns to optimize the conventional cosmetic procedures that cosmetic dermatologists/practitioners perform.

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