A SUPPLEMENT TO

JOURNAL OF DRUGS IN DERMATOLOGY

JDD

DRUGS • DEVICES • METHODS

The Periorbital Complex: Physical and Psychological Considerations for Non-Surgical Rejuvenation

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ISSN: 1545 9616

January 2014 • Volume 13 • Issue 1 (Supplement)

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This supplement to the *Journal of Drugs in Dermatology* is supported by an independent educational grant from Allergan Inc,

CME

EDITORIAL

ORIGINAL ARTICLES

THE PERIORBITAL COMPLEX: PHYSICAL AND PSYCHOLOGICAL CONSIDERATIONS FOR NON-SURGICAL REJUVENATION

Release Date: January 1, 2014
Termination Date: December 31, 2014
Estimated Time to Complete This CME Activity: 1 hour
Media/Method of Physical Participation: Journal article, web-based post-test, and evaluation
Hardware/Software Requirements: High speed internet connection, any web browser

Statement of Need

Facial ageing is a dynamic process; facial beauty is an important component of physical attractiveness and reflective of chronological age. A clear understanding of the anatomy of the periorbital complex is required to understand the natural ageing process, anatomical variations, and abnormalities in patients. Periorbital ageing is a relentless process that inevitably progresses over time and may have various psychosocial and functional effects. Techniques for rejuvenation of the periorbital complex have evolved dramatically in recent years and now include a variety of minimally invasive treatment options. Dermatologists need to keep abreast of the features, benefits, safety, and commonly encountered complications of these minimally invasive techniques, and require up-to-date, evidence-based information, and targeted educational opportunities.

Educational Objectives

This activity is a multi-specialty, evidence-based initiative designed to increase the knowledge and competence of dermatological practitioners by providing them with the simultaneous integration of knowledge, skills, and judgment from thought-leader testimonials, science-based research, and evidence-based data to address the difference between present patient outcomes and those considered achievable in the field of dermatology.

Upon completion of this activity, participants should be able to:

- Recognize the distinct underlying anatomy of the human orbital region.
- Differentiate normal orbital area structure and anatomic variations.
- State common anatomic changes associated with the normal aging process.
- Compare the features and benefits of minimally invasive rejuvenation techniques of the periorbital region vs cosmetic surgery based on patient selection and desired outcomes.
- Specify the appropriate use of neurotoxins and soft tissue fillers available for periorbital rejuvenation.
- Evaluate commonly encountered complications and adverse effects associated with injectable modalities for facial rejuvenation.
- Integrate evidence-based decision making into the dermatologic clinical transaction.

Target Audience

This activity is intended for dermatologists, residents in dermatology, and physician assistants who need continued education in the unique features of the periorbital complex and current strategies for rejuvenation and correction of anatomical variations.

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The peer reviewer has disclosed no relationships with commercial interests.

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Introduction

Kenneth R. Beer MD FAAD

"Eyebrows are important from both a psychological and a social perspective."

It is often said that the eyes are the windows to the soul, but, if this is the case, the eyebrows are the frames that define them. Recently, topical treatments for eyebrow hypotrichosis have enabled physicians to redefine this region. Topical bimatoprost has been demonstrated to improve the growth of eyebrow hair. When used in conjunction with botulinum toxins, light sources, topical cosmeceuticals, and fillers such as hyaluronic acid, the physicians' ability to treat this region has vastly improved.

Eyebrows are important from both a psychological and a social perspective. As Dr. Carruthers so elegantly discusses, they have been the focal point of fashion and aesthetics for centuries. Societal status has been defined by different eyebrow shapes in different societies at different times; but the eyebrows have always been critical to appearance.

Dr. Nguyen discusses the biology of brow hair to help explain how it grows. As with hair in other parts of the body, brow hair grows in cycles; however, it has receptors that make it amenable to treatment with prostaglandin analogues. An improved understanding of the biology of brow hair is likely to result in better treatments for eyebrows and perhaps lashes as well.

Treatments for the periorbital region have been improving over the past decade, and our ability to treat this area, as well as patient interest in these treatments, have increased in tandem. My article reviews treatments with botulinum toxins, lasers, fillers, cosmeceuticals, and bimatoprost. Combining these can produce dramatic results. However, treatments of the periorbital region also require a greater degree of skill and experience than do many other aesthetic treatments.

The goal of this supplement is to review our understanding of the biology of the hair in the periorbital region, the treatments available for aesthetic improvement of the periorbital region, and the social and psychological impact of the periorbital region.

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Social Significance of the Eyebrows and Periorbital Complex

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ABSTRACT

The eyebrow is simple to regard, but complicated to understand. Over the centuries it has been used as an indicator of social status, gender, and level of authority. In differing societies its descent and thinning with time have made it an important benchmark of the aging process. The brow is higher in the younger woman, but because of the loss of periorbital bone and fat starting in early middle age in women, the brow tends to descend, giving a tired, depressed, or anxious appearance. The brow in men is usually more resistant to downward movement until they are in their fifties. As a result, a whole industry has grown up around such varied techniques as plucking and redrawing, or gluing or tattooing on a replacement. In earlier centuries, the shaven forehead and almost absent brow were seen as a symbol of sexual purity. In the modern age, the brow is seen as an important part of facial recognition technology and is valuable in aspects of security and monitoring.

J Drugs Dermatol. 2014;13(suppl 1):s7-s11.

INTRODUCTION

If the eyes are the windows to the soul, the eyebrows must surely be the frames, shaping the face and giving definition to the eyes and forehead. Many women spend a great deal of time maintaining the appearance of the eyebrows, via plucking and shaping, cosmetics, or even surgical implants. Historically, fashionable trends revolved around thickness, hue, and the shape of the arch; and there is no doubt that eyebrows have always contributed significantly to the perception of facial attractiveness.

However, compared with other primates, modern humans are relatively hairless, so the persistence of the eyebrow over time is curious.[1] Do eyebrows merely represent evolutionary vestiges, or do they serve a greater, or more functional, purpose? Indeed, as one of the most powerful and versatile features of the human face, the eyebrow informs the perception of beauty and plays a critical role in sexual dimorphism, facial recognition, and non-verbal communication.

DISCUSSION

Muscular Anatomy of the Brow

The musculature of the brow has received intense study with the advent of brow treatments with neuromodulators and fillers. Three muscles—the corrugator supercilii, procerus, and depressor supercilii—work together to cause the head of the brow to rotate medially and descend in the frown.[2] The frontalis, the primary elevator muscle, raises the forehead and eyebrows medially and can elevate the eyelid as high as 5 mm at maximal action.[3] (Figure 1).

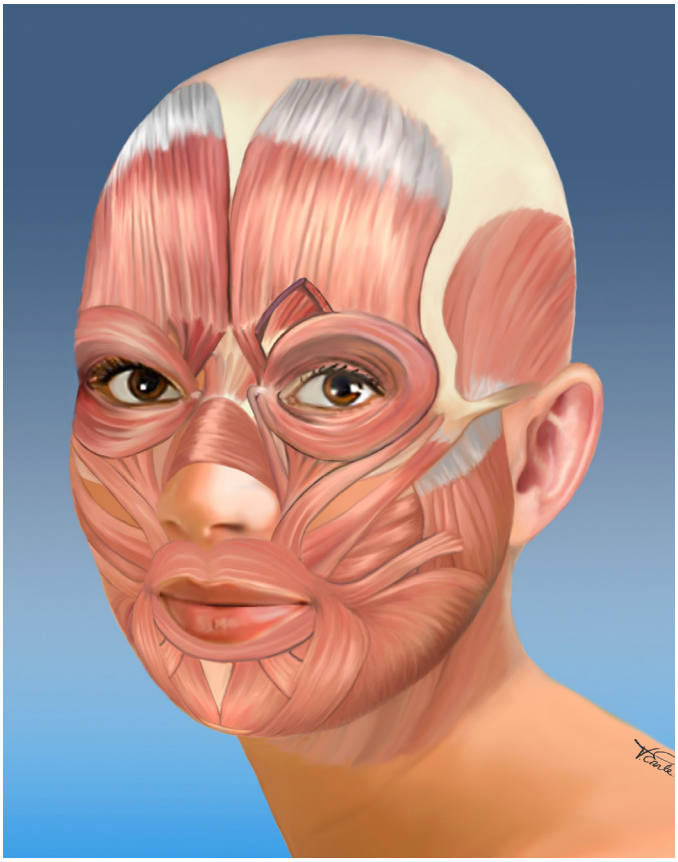
From the age of 25 in women and 45 in men, there is a progressive resorption of bone and fat in the periocular and perioral regions.[4] For the first time in history, brow position can be affected by voluntary medical injection treatments,[5] a trend that is summarized by the 4900.1% increase in injectable treatments seen from 1997 to 2012.[6] (Figures 2a and 2b.)

Evolution of the Brow

The supraorbital ridge, also called the supraorbital arch or supraciliary ridge, lies above the eye sockets and is common to all primates, including humans, although the size of the ridge varies between species.[7] Scientists refer to a more prominent ridge as the supraorbital torus, which presents as a continuous shelf of bone that projects above the orbits and nose and can be seen in our closest living relatives (the gorilla and chimpanzee), as well as in most fossil hominids (our ancestors). With the expansion of the cortex and development of the frontal lobe, the prominent brow gave way to the high, straight forehead of modern Homo sapiens, leaving behind only 2 hairy reminders of our evolutionary past along the lower margins of the ridge. What purpose do they serve?

Researchers believe the primary function of the eyebrow to be one of protection, the slope of the brow and arch drawing moisture or other debris around to the sides of the face. Because of their position and curvature, the eyebrows act as a shield against direct bright light, and stimulation of the hairs—abundantly innervated and sensitive to tactile stimulation—causes a reflex blinking of both eyelids.[8] But why did

FIGURE 1. Drawing of the muscles of periocular and facial expression.



nature select the emergence of eyebrows for extra protection over the maintenance of the supraorbital torus or prominent (and hairless) brow ridge? The answer may lie outside the scope of basic anatomy.

The Beautiful Brow

Like the hair on our head, our eyebrows, and in particular how we groom them, can say much about the time and place in which we live and have enormous influence on the perception of beauty and attractiveness. Over the centuries, eyebrows have been plucked into oblivion, shaved and repainted high on the forehead in bold slashes or delicate arches, removed and replaced with false eyebrows made from the fur of rodents or other animals, and attached with various types of glue.[9] Ancient Egyptians shaved or tweezed their eyebrows and then darkened them with gray or black powder made from a lead-based mineral, and classical brows were painted black with soot or powdered minerals or affixed with false brows made out of dyed goat's hair and tree resin. During medieval times in Europe, women favored skinny brows and plucked hairlines to achieve a high, domed forehead, a trend that continued into the reign of Queen Elizabeth I, when the pale, "egg-like" appearance denoted sexual and spiritual purity (Figure 3). Parents rubbed walnut oil into their children's eyebrows in an effort to

FIGURE 2a and FIGURE 2b. Before and after photographs of a botulinum toxin A treated brow.

prevent the growth of hair. In China, the Ming Dynasty empresses were very aware of the age-related descent of the brow, so they shaved or plucked and carefully drew their brows back on but placed higher on their foreheads.[9] (Figure 4).

> "As one of the most powerful and versatile features of the human face, the eyebrow informs the perception of beauty and plays a critical role in sexual dimorphism, facial recognition, and non-verbal communication."

In the seventeenth and eighteenth centuries, bold brows made a comeback as a symbol of youth. However, the same make-up used to whiten a good lady's face and conceal unsightly pockmarks and pitting—ceruse, a mixture of white lead and vinegar—caused women to lose their eyebrows, among other unfortunate side effects.[10] To compensate, women would trim

FIGURE 3. Queen Elizabeth I. Shaved anterior hairline and brows give the impression of "egg-like purity".

FIGURE 4. Ming dynasty Empress with eyebrows redrawn higher on the forehead. Ming dynasty tombs, China.

scraps of mouse or rat pelts (caught from nightly traps) into glossy fake eyebrows that had a terrible habit of coming unglued at inopportune times.

In 1915, a young entrepreneur named Tom Lyle Williams watched his sister, Mabel, fix her singed eyebrows with a mixture of Vaseline, ash, and coal dust, and tried to recreate a similar product using petroleum, carbon black, cottonseed oil, and safflower oil.[11] When his first effort with the chemistry set failed, he teamed up with drug manufacturer Parke-Davis, eventually marketing a scented, colorless cream with petroleum and oils that promised to nourish and promote the growth of eyelashes and eyebrows—although he noted that 2 to 3 boxes were needed before any noticeable improvement—under the name Maybell Laboratories. He later renamed his company Maybelline, and a world of cosmetics opened up.

Since then, eyebrow fashions have cycled through skinny vs fat, arched vs straight. Arresting, impeccably groomed eyebrows of the fifties followed the anorexic arches of the twenties, and were followed in turn by thick and thin versions over the years.[9] In the film and fashion world, eyebrows had become a unique calling card. Witness Audrey Hepburn's dark, straight brows, the thick and sultry arches of Marilyn Monroe and Elizabeth Taylor, or Frida Khalo's defiant uni-brow. Sophia Loren shaved her brows and drew them back in using excruciatingly detailed strokes.[9] All of them were instantly recognizable.

Facial Recognition

It has always been assumed, and demonstrated, that facial recognition depends primarily on the eyes.[12-14] In the sixties, Professor Desmond Morris studied eye movement recordings demonstrating that the observer's line of sight roves from the subject's periocular region down to their mouth, and back up to the area of the eye.[15] His studies emphasized the importance of the interpersonal analysis of the emotional and social context of a face.

Historically, the brow ridge in the periocular region may have been an important sexually distinctive characteristic of our

early ancestors' faces: with higher levels of testosterone, men naturally have more pronounced brow ridges and eyebrows, angular jaws, and thick facial hair. Recent studies have found an important role for eyebrows in discriminating between male and female faces. Bruce and colleagues found that eyebrow thickness and position aid in gender differentiation, with thinner brows that are higher above the eye for women compared with men.[16,17] Prior studies examining the key markers of facial recognition identified a hierarchy of key identifying features, with the eyes as the most important, followed by the mouth and the nose.[12-14] Eyebrows were disregarded entirely or grouped together with the eyes.[13] However, a more recent study demonstrates that the absence of eyebrows significantly impairs the ability to recognize familiar faces to a greater degree than the absence of eyes.[18] Sadr and colleagues altered 50 photographs of celebrities using a feature omission technique in which the eyes (25 images) or eyebrows (25 images) were digitally removed while retaining the color and texture of the skin for minimal visual disruption.[18] Eighteen subjects examined photographs from each set and were able to recognize 55.8% of images without eyes, but only 46.3% without eyebrows.

Communication and Emotional Response

No other feature of the face is so easily modified or so powerful as a visual form of communication. Throughout history, eyebrows have had the uncanny ability to demonstrate much without saying a word. Consider the exaggerated arches of the silent film stars like Greta Garbo that conveyed every twitch of emotion on camera. Those brows were serious; those brows were meant to speak in the absence of voice. As research has shown, eyebrows are a language unto themselves.

Indeed, the position of the eyebrows—elevated, depressed, or drawn together, all dependent on the interplay of elevators and depressors—is critical for emotional expression. Changes to the angle, height, and curve of the eyebrow, alone or in combination with other facial movements, can produce a broad range of signals across the spectrum of human emotion that radically alter the expression of the face and serve as nonverbal forms of communication to convey emotion.[18] Maximal elevation of the medial and lateral portions of the eyebrows results in a look of surprise, depression of the medial portion depicts anger or concern, and the raising of a single eyebrow denotes a quizzical or questioning expression.[8]

Ekman and Friesan, pioneers in the measurement of facial expression, compartmentalized the face into 3 regions—upper (eyebrows, forehead), middle (eyes, cheekbones), and lower (mouth, nose, and chin)—and found that the eyebrows play a key role in the expression of a number of universal emotions, including happiness, surprise, and anger.[19-23] Moreover, of the 7 visibly distinctive eyebrow actions, 5 are involved in emotional expressions, while the other 2 play a major role in a variety of conversational signals, whether on the part of the speaker or listener.[22] In American Sign Language, a signed statement automatically becomes a question with the addition of raised eyebrows.[24] The eyebrow flash is a universally recognized, yet unconscious, social signal across all primates and cultures, comprising a quick (approximately one-sixth of a second) up-and-down movement in recognition and greeting, preparing the user (and receiver) for social contact.[25] Similarly, raised eyebrows during speech can signal questions, emphasize or accentuate a word or phrase, and serve as punctuation, while the brow movements of a listener may denote seriousness, importance, doubt, perplexity, or difficulty in comprehension, among other signals.[18]

"Throughout history, the appearance of the brow has always been important, but recent research has shown that the role of the eyebrow in emotional expression defines dominance, emotion, gender, or adherence to modern fashion."

CONCLUSION

Eyebrow fashions change with the ages. In ancient Egypt, both men and women displayed natural full eyebrows. In the Middle Ages in Europe, in the age of Chivalry, the brow was seen to be important sexually, and it became fashionable for attractive women to shave or pluck their eyebrows as well as their anterior hairline to produce a pale, egg-like appearance considered appropriately demure. In the last 100 years, women have commonly altered or enhanced the shape of the eyebrows by plucking them into fine arches, a trend currently considered unnatural. Brow experts teach women how to shape their eyebrows for a fuller and more youthful look, aided by topical hair-growth products, cosmetic powders, pencils, tattoos, and even transplants.

Throughout history, the appearance of the brow has always been important, but recent research has shown that the role of the eyebrow in emotional expression defines dominance, emotion, gender, or adherence to modern fashion. It may be argued that today the brows have a greater social significance as powerful markers of facial recognition and multipurpose signalers, able to communicate a wide range of emotion and messages, to amplify verbal messages, or, even better, to communicate without saying a word.

DISCLOSURES

Jean Carruthers MD FRCSC FRC (OPHTH) and Alastair Carruthers MD MRCP FRCPC have served as consultants and researchers for Allergan Inc, American Society of Dermatologic

Surgery, Fortis Spectrum, Gerson Lehrman Group, Kythera-biopharma, Merz GmBH, MerzUSA, Ogilvy CommonHealth Worldwide, TKL Research, and TogoRun.

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The Biology, Structure, and Function of Eyebrow Hair

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ABSTRACT

Eyebrow hair serves many important biologic and aesthetic functions. This article reviews the structure and function of the hair follicle, as well as hair follicle morphogenesis and cycling. Eyebrow hair follicles share the same basic structure as hair follicles elsewhere on the body, but are distinguished by their shorter anagen (growing) phase. Knowledge of the hair follicle structure and cycle is important for understanding the pathophysiology of alopecia, as diseases affecting the stem cell portion of the hair follicle in the bulge region may cause permanent hair loss. Furthermore, therapeutic agents that target distinct phases and hormones involved in the hair cycle may be useful for promoting hair growth.

J Drugs Dermatol. 2014;13(suppl 1):s12-s16.

INTRODUCTION

Skin and hair possess many important biologic functions, serving as the body's first line of defense against the outside world. In continuity with the skin, the hair follicle functions to protect the skin from the environmental elements and disperses sweat gland products (eg, pheromones).[1] Eyebrow and eyelash hair protect the eyes from sweat and moisture. In addition, the hair follicle transmits sensory information to the nervous system via neuroreceptors that respond to mechanical stimuli above the skin surface. Hair also has essential immunologic functions, as Langerhans cells at the opening of the follicle detect surface pathogens and stimulate the immune system, in conjunction with perifollicular immune cells such as macrophages and mast cells.[1]

Furthermore, hair holds aesthetic importance, and conditions that result in hair loss (alopecia) or excessive hair growth can have devastating psychosocial effects. Eyebrows are vital for facial expression and, in conjunction with the eyelashes, cheekbones, hairline, and nose, eyebrows frame the eyes, thereby contributing to an individual's unique facial appearance.

DISCUSSION

Structure of Hair Follicles

Although hair follicles on the body vary in size and shape, they all share the same basic structure. The lower portion of the hair follicle comprises the hair bulb, which is composed of rapidly proliferating matrix cells that produce the hair shaft. The epithelial component of the hair follicle is composed of at least 8 concentric layers: the outer root sheath (ORS), the companion layer, the inner root sheath (IRS), which is subdivided into Henle's layer, Huxley's layer, and the cuticle of the IRS, and the hair shaft cuticle, the cortex, and the medulla (Figures 1 and 2). These layers are composed of characteristic intermediate filament keratins, enzymes, and adhesion molecules.[2] The ORS of the hair follicle is continuous with the epidermal basal layer and contains melanocytes, Langerhans cells (dendritic antigen-presenting cells), and Merkel cells (specialized neurosecretory cells).[1]

Pigment in the hair shaft is produced by melanocytes located in the hair bulb that transfer melanin to keratinocytes in the developing hair shaft cortex and medulla. As the matrix cells differentiate and move upward, they are compressed by the rigid IRS, whose structure determines the shape of the hair shaft.[1] The dermal papilla, which is composed of specialized mesenchymal cells located at the base of the follicle, is thought to control the proliferation of matrix cells and thus the size of the hair shaft.[1]

The bulge consists of a cluster of biochemically distinct cells located in the ORS, near the insertion of the arrector pili muscle. Bulge cells have the characteristic properties of epithelial stem cells: they are slow-cycling (quiescent) and are thought to persist for the lifetime of the hair follicle.[3,4] It is believed that the bulge population contributes to epithelial cells that proliferate and regenerate the new lower follicle during the growing stage of the hair cycle. Epithelial stem cells in the bulge portion of the ORS may also serve as a reservoir for epidermal and sebaceous-gland cells.[5,6] The bulge region of the hair follicle is especially rich in nerve endings and Merkel cells.[1] Hair follicle bulge cells express CD34 in mice and keratin 15 in humans.[3]

Morphogenesis of Hair Follicles

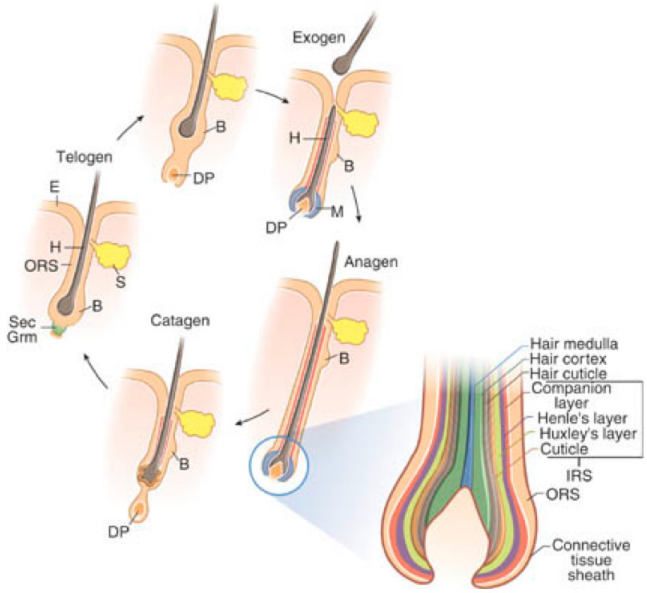
Hair morphogenesis is initiated in utero through complex interactions between the epithelium and underlying dermis.

An array of activating and inhibitory secreted molecules orchestrates follicular induction. The initiating signal is thought to arise from the dermal mesenchyme, which induces hair-follicle formation from the overlying epithelium during fetal development. The Wnt/β-catenin pathway is thought to be integral to this process, as it is first upregulated in the upper dermis, initiating the downgrowth of keratinocytes from the epithelium to form the epithelial hair follicle placode.[7,8] In the presence of a Wnt signal, cytoplasmic β-catenin translocates to the nucleus where it forms a transcription complex with deoxyribonucleic acid (DNA) binding factors of the lymphoid enhancer-binding factor/T-cell factor (LEF/TCF) family, and activates transcription of target genes.[7] An epithelial signal from the placode (likely Wnt and platelet-derived growth factor-A molecules) promotes the clustering of underlying mesenchymal cells, forming a dermal condensate.[7] Sonic hedgehog, a secreted protein downstream of Wnt signaling, is required for the proliferation of follicular epithelium and development of the dermal condensate into a dermal papilla.[7] In response to a signal from the dermal condensate, the epithelial placode cells proliferate and invade the dermis, eventually surrounding the dermal condensate, forming the hair follicle dermal papilla.[7,9] In addition to hair follicle morphogenesis, Wnt signaling is essential during the adult hair cycle, as Wnt activity is observed in the secondary hair germ during anagen onset and in the precortex of anagen follicles during hair shaft differentiation.[10]

Other genes that are thought to play a role in the spacing and distribution of the follicles during early morphogenesis include lymphoid enhancer-binding factor-1 (LEF1), bone morphogenetic protein 4, and the type II receptor for transforming growth factor β.[1,7] Ectodysplasin-A receptor (EDAR), fibroblast growth factor receptor, and bone morphogenetic protein receptor signaling contribute to hair follicle specification and patterning.[11] Reciprocal epithelial-mesenchymal interactions promote hair follicle differentiation and maturation of the adjacent dermal papilla, which becomes enveloped by proliferating matrix cells that differentiate into the IRS and hair shaft. The ORS is continuous with the epidermal basal layer and grows downward.[11] Hair follicle stem cells are thought to arise early during hair morphogenesis at the placode/germ stage. The stem cells localize to the upper ORS during development, forming the hair follicle bulge.[11]

Hair follicle development progresses in cephalocaudal direction, becoming first visible in the eyebrows, upper lip, and chin regions at 9 weeks of gestation, with the formation of hair shafts at 16 weeks.[12] Approximately 5 million hair follicles cover the human body at birth.[1] Although the number of hair follicles does not increase after birth, the size of the follicles and hairs can change (eg, transition of vellus to terminal hairs under the influence of androgens).

FIGURE 1. Hair follicle cycling and anatomy. The 4 stages of hair follicle cycling are follicle growth (anagen), regression (catagen), rest (telogen), and hair shedding (exogen). Matrix cells in the bulb generate 7 different hair follicle layers.



B, bulge; DP, dermal papilla; H, hair; IRS, inner root sheath; M, matrix; ORS, outer root sheath; S, sebaceous gland; Sec Grm, secondary germ. Reprinted with permission from Blackwell Publishing, Inc. *Journal of Investigative Dermatology*. 2006;126(7):1459-1468. ©2006.

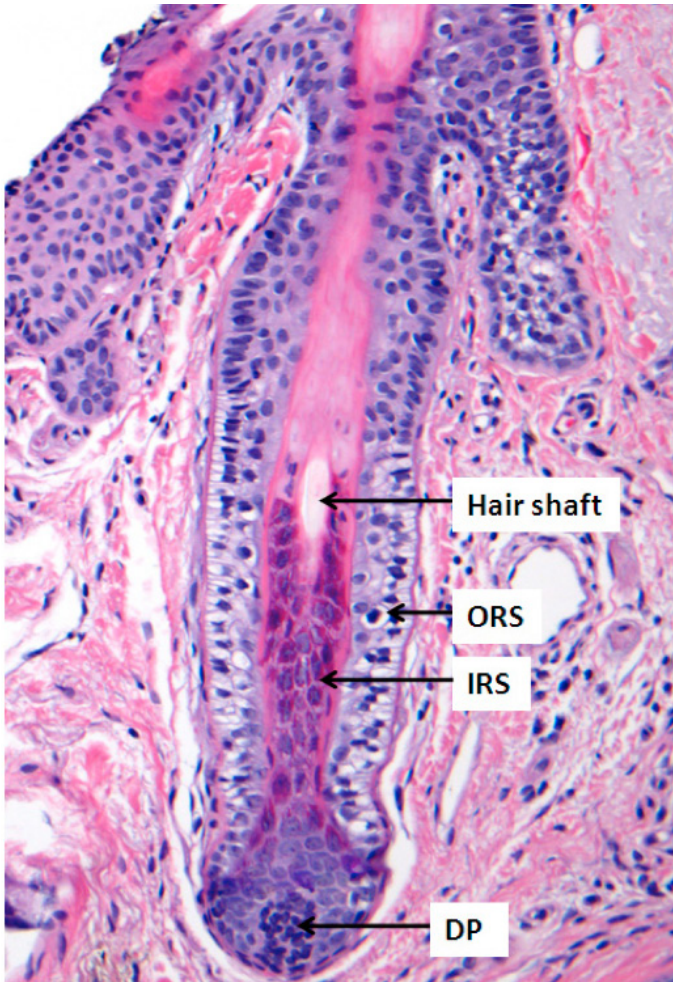
Hair Follicle Cycling

The hair shaft is continuously regenerated in a cycle that consists of 4 stages: hair follicle growth (anagen), regression (catagen), rest (telogen), and hair shedding (exogen) (Figure 1). The entire lower epithelial structure is formed during anagen, during which matrix keratinocytes in the bulb of the lower follicle rapidly proliferate. The duration of anagen is proportional to hair length. For example, human eyebrow hair follicles are short because they stay in anagen for only 2 to 4 weeks,[3] while scalp follicles have the capacity to grow long because they can remain in anagen for many years.

The lower portion of the hair follicle regresses during catagen, which occurs through programmed cell death (apoptosis) of follicular keratinocytes as well as melanocytes. Catagen usually lasts 2 to 3 weeks. Toward the end of the catagen stage, the dermal papilla condenses and moves upward, coming to rest underneath the hair follicle bulge.

During the telogen stage, the hair shaft matures into a club hair. Telogen typically lasts for 2 to 3 months. The percentage of follicles in the telogen stage varies substantially according to the region of the body (eg, 5% to 15% of scalp follicles are in the telogen stage at any one time, as compared with 40% to 50% of follicles on the trunk).[1] An increase in the percentage of scalp follicles in the telogen stage leads to excessive shedding.

FIGURE 2. Histology of eyebrow hair.



DP, dermal papilla; IRS, inner root sheath; ORS, outer root sheath.

After telogen, the lower, hair-producing portion of the follicle regenerates. As the new hair shaft grows in, the old hair is shed during exogen, and the cycle is repeated.

The exact molecular mechanisms of hair follicle cycling are still being elucidated, and numerous growth factors and growth factor receptors are implicated. Stem cells from the bulge region are believed to be integral to the initiation of anagen and formation of the new hair shaft with each hair cycle. The onset of the anagen stage recapitulates hair follicle development, as the formation of the new lower hair follicle is initiated by signals derived from secondary germ cells. Secondary germ cells are found at the base of the telogen follicle, and are believed to arise from the lowermost portion of the bulge at the end of catagen.[13] During late telogen/anagen onset, the dermal papilla stimulates secondary hair germ cells to proliferate, which initiates hair growth and generates the matrix, IRS, and hair shaft. The bulge cells respond by undergoing activation and proliferation later, during the anagen phase. The bulge cells continue to cycle slowly during the anagen phase to extend the ORS and maintain the matrix to support hair growth.[14] Many of the mesenchymal-epithelial interactions and secreted signaling molecules critical for hair follicle morphogenesis, such as Wnt ligands and Sonic hedgehog, are required to promote anagen onset and hair follicle growth during the adult hair cycle. The cessation of the anagen stage is controlled by various factors, including epidermal growth factor and fibroblast growth factor 5, which is first expressed in the follicle just before the end of this stage.[5]

The most common hair disorders are related to aberrations in hair follicle cycling. Telogen effluvium manifests as a transient period of hair shedding, often associated with medications, fever, endocrine abnormalities, parturition, anemia, and malnutrition. It occurs when an increased number of hair follicles prematurely enter the telogen stage, resulting in subsequent hair shedding. Transient shedding typically begins 2 to 4 months after the inciting event and lasts for several months.[1] Hair regrowth usually follows, assuming the precipitating trigger is removed. Telogen effluvium is typically limited to the scalp, but may affect other areas, such as the eyebrows or pubic region.

> "Prostaglandin analogues, such as bimatoprost, have been shown to induce eyelash growth, although the mechanism is unclear."

Hormones Controlling Hair Growth

Many hormones play a role in controlling hair growth, the most significant of which are androgens. Androgens contribute to the most common type of hair loss, androgenetic alopecia (AGA), eg, male and female pattern hair loss. Androgenetic alopecia is due to the progressive miniaturization of the hair follicle (transition from terminal hairs to vellus hairs) and shortening of the anagen cycle duration. This miniaturization is due to testosterone and its active metabolite, dihydrotestosterone, acting upon androgen receptors in the dermal papilla.[1] These hormones convert vellus hairs to terminal hairs in androgen-dependent areas such as the beard, axillary, and pubic areas during adolescence, yet later in life they can cause miniaturization of follicles in the scalp (resulting in AGA).

The conversion of testosterone to the more potent dihydrotestosterone is catalyzed by the enzyme 5α-reductase (types I and II). The type I enzyme is found predominantly in sebaceous glands and the liver, and the type II enzyme is predominant in hair follicles of the scalp, beard, and chest, as well as in the liver and the prostate gland. Finasteride, which inhibits 5α-reductase type II, slows the progression of AGA by inhibiting 5α-reductase.

Other hormones that modulate hair growth include estrogens, thyroid hormones, glucocorticoids, retinoids, prolactin, and growth hormone.[1]

Minoxidil has been used for patients with severe hypertension and was incidentally observed to result in hair growth. The mechanism by which minoxidil induces hair growth is not fully elucidated, but may be related to its action on opening of the adenosine triphosphate (ATP) sensitive potassium channel (K[ATP] channel). K(ATP) channel opening in dermal papilla cells at the base of the follicle is thought to play a role in stimulating hair growth.[15] As a vasodilator, it may promote more oxygen, blood, and nutrients to the proliferating dermal papilla cells. Other studies have shown that minoxidil stimulates the production of growth factors such as vascular endothelial growth factor in cultured dermal papilla cells, and that these growth factors might stimulate hair growth.[16] It has also been shown that minoxidil promotes the survival of human dermal papilla cells, thereby prolonging anagen, through proliferative and anti-apoptotic effects.[17]

Prostaglandin analogues, such as bimatoprost, have been shown to induce eyelash growth, although the mechanism is unclear. It is suggested that hypertrichosis is probably a result of the induction of the anagen phase in the telogen phase follicles of the eyelashes and prolonging the anagen phase.[18] Anecdotal cases describe significant eyebrow hair growth after use of topical prostaglandin analogues for eyebrow hypotrichosis.[19]

"Knowledge of the hair follicle structure and cycle is key to understanding the pathogenesis of the different types of alopecia, as well as developing targeted therapies for hair loss."

Other Hair Follicle Disorders

In contrast to AGA, hirsutism and hypertrichosis result from a prolonged anagen stage with an abnormal enlargement of hair follicles; small, fine vellus hairs transform into large, terminal hairs. This can be caused by medications or hormonal factors (eg, dysfunction in the adrenal glands or ovaries resulting in hyperandrogenism).

Anagen effluvium is caused by the cessation of anagen, often due to antineoplastic/chemotherapeutic drugs, which disrupt the rapidly proliferating bulb matrix cells. As a result, the hair shaft becomes narrower, with subsequent breakage and loss of the hair. Because the stem cells of the hair follicles are typically spared, a new hair bulb may be regenerated once the medication is stopped. Hair loss usually begins 1 to 2 weeks after chemotherapy is started and is most noticeable by 1 to 2 months.[20] The scalp hair is usually most affected, but all body hair, including eyelashes and eyebrows, can be affected.[21]

Inflammatory alopecias (such as lichen planopilaris and discoid lupus erythematosus) can lead to permanent scarring hair loss, whereas others (such as alopecia areata and telogen effluvium) are nonscarring and potentially reversible. In scarring alopecias, the inflammation usually involves the superficial portion of the follicle, including the bulge area, resulting in permanent destruction of the stem cells necessary for the regeneration of the follicle. In contrast, the acute follicular inflammation in alopecia areata targets the hair bulb in the subcutaneous fat, resulting in disruption of the anagen stage. Because the bulge area is spared, the hair follicle has the potential to generate a new hair bulb and hair shaft once the inflammation has resolved.

Hair disorders associated with rare congenital hair defects, such as Netherton's syndrome and ectodermal dysplasias, are caused by mutations in keratins or other structural proteins. Netherton's syndrome is an autosomal recessive disease caused by mutations in serine protease inhibitor Kazal-type 5, encoding the serine protease inhibitor lympho-epithelial Kazal-type-related inhibitor. It presents with an atopic diathesis, allergic reactions, and icthyosiform dermatitis. A clue to diagnosis is the examination of eyebrow hairs, which will characteristically show trichorrhexis invaginata, in which the distal portion of the shaft is invaginated into the proximal portion.[22] Eyebrows may be the sole site of involvement in many patients with Netherton's syndrome, and the findings more prominent than in the scalp.[22]

CONCLUSION

In summary, eyebrow hair serves many important biologic functions, including sensory transmission and protection from the elements, as well as playing an important role in cosmesis and expression. The hair follicle originates from complex mesenchymal-epithelial interactions during embryogenesis. Similar molecular mechanisms underlie hair follicle cycling during one's lifetime. Knowledge of the hair follicle structure and cycle is key to understanding the pathogenesis of the different types of alopecia, as well as developing targeted therapies for hair loss.

DISCLOSURES

Jennifer V. Nguyen MD has no conflicts of interest to disclose.

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Aesthetic Treatment Considerations for the Eyebrows and Periorbital Complex

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ABSTRACT

The periorbital complex is a critical cosmetic unit. Treatments for this region range from topical prescriptions to enhance the brow hair to topical cosmeceuticals that improve the tone and texture of the skin. Lasers, radiofrequency, botulinum toxins, fillers, and a host of other treatments are used to treat the periorbital region. Judicious use of these treatments, alone or in combination, can greatly alter the appearance of the region. However, adverse events may also be associated with these treatments, and the clinician and patients need to consider both the risks and the benefits of treatment prior to embarking upon a regimen.

J Drugs Dermatol. 2014;13(suppl 1):s17-s20.

INTRODUCTION

The periorbital complex includes the eyelids, eyelashes, eyebrows, and bony structures that surround the eye. Aesthetic treatments for the periorbital region have been a cosmetic concern since the time of the early Egyptians, at which time various dyes were used to enhance the lashes and brows, and to accentuate the eyes. Since then, there has been significant progress. The advent of botulinum toxins for the treatment of glabella furrows heralded a new focus on this region, and at the present time botulinum toxin is the most popular minimally-invasive cosmetic procedure in the United States.[1] Soft tissue augmentation is used to renovate both the infraorbital region and the supraorbital region. Bimatoprost has been approved for the treatment of eyelashes, and recent publications have documented its efficacy for eyebrow hypotrichosis.[2] Radiofrequency and lasers have been used to both tighten and improve the quality of the skin, while topical cosmeceuticals have also been effective in some instances. The periorbital region is an important component of communication between individuals and is often the first area to show signs of aging. Patients thus often view it to be of socially significant concern.

DISCUSSION

Periorbital Aging

In order to understand what occurs in the periorbital region with aging, it is helpful to have some parameters of a youthful brow position and shape in a youthful face and to know how the soft tissue and bony structures of this area change with time. The eyebrows, composed of thick, pigmented terminal hair, not only protect against rain and sweat but also serve to express emotions, communicate, and contribute to differentiation between males and females.[3] The eyebrows serve as a site for both frontalis insertion and interdigitation with the orbicularis oculi. A fat pad exists in a split in the muscle sheath, allowing for eyebrow movement, and continues into the upper lid.[4]

In many people, the brow descends with age. This occurs as the elasticity of the forehead region decreases and the frontalis is no longer able to suspend the brow. With this descent of the brow, there is less suspension of the upper eyelid, which tends to droop. One study of the aging brow in Indian women found that, in the population studied, with age the lateral brow descended while the medial brow stayed relatively constant.[5] These authors recommended "brow reshaping by restoration of the brow apex lateral to the level of the outer corneal limbus" as a goal for cosmetic rejuvenation of the periorbital area. This goal may be attained surgically provided that the patient is a candidate for surgery and amenable to the procedure. However, many patients prefer not to have this region addressed surgically if an alternative is available.

In addition to these changes noted in the soft tissue, there are significant changes in the bony structures of the periorbital region. A CT evaluation of 60 women and 60 men found a significant increase in the orbital width and aperture with aging,[6] a change that was noted in both sexes and is thought to be one hallmark of the aging periorbital region. In addition to the profound changes that are seen within the bony structures of the periorbital region, there are other significant changes in the soft tissue, as well as in the fat and hair of these areas. A comparison of aging in the periorbital area soft tissue using CT scanning demonstrated that the soft tissue muscle volume in the periorbital area decreased in women but increased in men.[7] These same authors found an increase of periorbital fat volume in women as they age. Another change that occurs with the aging brow is a decrease of the den-

sity and color of the eyebrow hair. This tends to shift the aesthetic focus away from the periorbital area.

Treatment Considerations

With the advent of botulinum toxins, lasers, energy devices, and lash and brow topical treatments, there are alternatives to surgery that allow impactful non-surgical approaches.

Botulinum Toxins

Type A botulinum toxin treatments remain a popular option for improvement of the periorbital complex. In the United States, there are 3 type A toxins approved for use in the glabellar region, but only one of these is approved for the treatment of the orbicularis oculi muscles. Injections of botulinum toxins may be used to raise or lower the brow. Injections into the depressor muscles of the glabella complex without treatment of the brow elevator (the frontalis) will enable the brow to elevate. This "brow lift" may be titrated based on patient anatomy to shape the brow and, to a lesser degree, the upper eyelid. This elevation may be further enhanced by injections of toxins into the depressor potion of the orbicularis oculi muscles.

Injections of onabotulinumtoxinA (Botox®) into the glabella region use 20 to 25 units of toxin to decrease the activity of the procerus and corrugator muscles. This same injection may be performed using abobotulinumtoxinA (Dysport™) by using 50 to 60 units of toxin, whereas the use of incobotulinumtoxinA (Xeomin®) for this treatment requires about 25 to 30 units. Use of the correct amount of toxin will not only help to decrease the appearance of vertical glabellar lines but also minimize the depressor component of the procerus, which will help to raise the brow to a more youthful appearance. These injections have been demonstrated not only to improve appearance, but also to improve self-esteem and lower the perceived ages of those treated.[8-10] Optimal correction of static glabellar lines requires concomitant use of a hyaluronic acid (HA). The use of fillers combined with toxins not only helps to improve the appearance but also increases the duration of this correction.[11,12]

Botulinum toxins may also be used to treat the lateral periorbital region to decrease the appearance of the so called "crow's feet". Injections into this area may use 40 to 60 units of abobotulinumtoxinA, 20 to 30 units of onabotulinumtoxinA, or 25 to 35 units of incobotulinumtoxinA to treat both sides. When injected properly, the wrinkles that surround the lateral periorbital region may be markedly diminished and the depressor component of the lateral orbicularis orbiti muscle may be minimized. This latter action enables the lateral brow to rise and helps to position the brow into a more youthful position (Figure 1). Injections of onabotulinumtoxin into the lower eyelid, 4 mm below the ciliary line, produced improvement of the lower lid rhytids; and it is likely that injections of other toxins into this area would yield similar results.[13]

FIGURE 1. The youthful periorbital region has the superior aspect of the brow directly above the lateral iris. There is no evidence of photodamage or laxity.

FIGURE 2. In the aging periorbital region, the brow and lid have descended, the lashes and eyebrow are more sparse and lighter in color, and the lid and periorbital skin have more rhytids and photodamage. Each of these issues may be addressed and corrected.

Lasers and Energy Devices

Devices that deliver energy to the skin of this region may also be used to alter the laxity of this area. Radiofrequency devices have been shown to tighten the skin of the brow as well as the skin of the lateral eyelid.[14,15] Recently several other devices including ultrasound have been used to tighten the skin of this periorbital region.[16,17] Lasers such as the carbon dioxide (CO_2) and erbium lasers may also be used to alter the laxity and the texture of the upper and lower eyelids.[18-20] The use of an energy-delivering device in this area requires a great deal of caution

and experience to avoid complications such as scarring, nerve injury, and/or ectropion.

As these devices have evolved, they have become more effective at producing meaningful results. For many patients, they may help significantly to improve the aesthetic appearance of the skin in this region. Carbon dioxide lasers have been demonstrated to improve the laxity and texture of the periorbital skin.[20] In addition to CO_2 lasers, ultrasound and radiofrequency are effective modalities to help tighten the skin of the periorbital area.[21] Many different commercial devices are available, and both monopolar and bipolar radiofrequency devices are effective at tightening the skin in this area. Treatments for this area must be sensitive to the fact that high energy delivered by any device may result in complications including ectropion (especially seen with aggressive laser or chemical peeling) and nerve damage (transient) from radiofrequency.

"The periorbital region is an important component of communication between individuals and is often the first area to show signs of aging."

Soft Tissue Augmentation

Soft tissue augmentation of the periorbital region was initially advocated solely for the infraorbital zone. However, as techniques and materials have improved, injections into other areas such as the brow and temple have become more prevalent. A prominent tear trough may be genetically predisposed or may evolve as the mid-face and periorbital fat pads sag and the ligaments become lax. In order to improve the tear trough deformity, materials such as autologous fat and HA have been successfully used. Attempts to use other products such as poly-L-lactic acid or calcium hydroxylapatite have met with less success and these materials should not be injected into the tear trough. Materials such as Restylane®, Juvederm®, and Belotero® are used to fill the deformity and re-inflate the lower tear trough. When injecting these products, technique is critical. If the HA is not placed in a deep plane, one runs the risk of seeing the product reflecting light and having a Tyndall effect, whereby the material appears as a blue bleb.[22] The correct plane to inject is the periosteal plane, below the orbicularis oculi muscle.

Injections should be conservative, especially in a patient who has not had prior treatment in this location. For the initial injection, it is reasonable to inject 1 mL shared between both sides. If there is a significant volume loss in the lateral compartment, a second mL may be injected. Injections of the tear trough should not transgress the orbital rim. To achieve optimal results, one should continue the injection of material laterally to support the lateral trough. Injections into the radiating periorbital rhytids may be performed using small amounts of reconstituted HA products. This dilution of product will change the physical characteristics of the gel and may help to minimize the appearance of blue gel blebs.

Injections of HA, poly-L-lactic acid, and calcium hydroxylapatite have been successfully used to fill the temporal fossa. These injections may help to improve the periorbital area by elevating the lateral brow. The lateral brow may also be injected with HA, in which case the needle should be inserted into the periosteal plane, taking care to avoid any vasculature. As with injections into the tear trough, one should be conservative with the volume injected.

Topical Products

Topical products to improve the appearance of this region now include prostaglandin analogues that not only increase the length and width of the eyelashes but also improve the length and girth of eyebrow hair. Use of bimatoprost daily resulted in an improvement of eyelashes in 78.1% of subjects after 16 weeks.[23] While this may not appear to be a major contributor to the aesthetics of the periorbital region, patient satisfaction with the improvement was significant. Bimatoprost has also been successfully used to improve the eyebrow hair.[24]

Prescription and non-prescription products are a frequent adjunct to treatments in this location. Tretinoin has long been used to decrease periorbital rhytids and may also help decrease hyperpigmentation.[25] Cosmeceuticals containing retinol, growth factors, antioxidants, and a host of other ingredients have also been shown to help to improve fine lines and dyschromia of the periorbital region.[26]

Complications

Complications can occur with each of these treatments. While most adverse events related to injection of botulinum toxins and fillers are related to injection trauma and include bruising, erythema, and swelling, some injections of botulinum toxins may result in ptosis or brow drop when the suspending musculature is relaxed.[27,28] Injections of toxins into the lower lid may relax the muscle pumping action sufficiently to produce ballooning of the lower lid in a patient who has had prior eyelid surgery.[29]

Fillers such as HA can have adverse events such as lumps and bumps, but can also have some serious and permanent complications including blindness, which can occur from vasculature occlusion.[30] Injections of fillers into the tear trough may produce significant periorbital edema, and the use of oral steroids may be helpful for minimizing this. Volumizers such as poly-L-lactic acid may cause subcutaneous papule formation, while calcium hydroxylapatite CAHA may result in bumps and white nodules when it is placed in the periorbital region.[31] Lasers, intense pulsed lights, and radiofrequency devices may produce

burns, changes to pigment, and other complications that may scar the periorbital region. As mentioned previously, radiofrequency energy may result in transient nerve damage.[32] Nerve damage that has been reported has been temporary and is believed to have resulted from the supraorbital nerve being trapped between the bony skull and the transducer. Chemical peeling agents used for the periorbital area have resulted in cicatricial ectropion, hyperpigmentation, hypopigmentation, and scarring. Topical agents such as bimatoprost and topical cosmeceuticals may cause irritation and hyperpigmentation.[33] Thus, treatment of the periorbital region is not without risk, and practitioners need to be aware of the potential for damage when they are treating this region.

CONCLUSION

The periorbital region is a critical cosmetic unit for human appearance. New technologies to tighten and resurface the skin, to grow the hair of the eyelashes and eyebrows, to smoothen and lighten the skin, and to replace volume lost from this area have created opportunities for rejuvenation that were not possible until recently. When treating this area, optimal outcomes may be attained by combining modalities and products and addressing each of the underlying issues. The psychological, aesthetic, and social impact of periorbital rejuvenation is only now being fully appreciated as treatments for this region have improved.

DISCLOSURES

Kenneth R Beer MD FAAD has served as a consultant, investigator, and speaker for Allergan Inc, Valeant, Kythera, and Anterios, and is a shareholder of Theraplex LLC. Stephanie Bayers BSBA and Jacob Beer have no conflicts of interest to disclose.

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1. What emotional effect does an eyebrow not give to the human face?
   a. Humor
   b. Sadness
   c. Dominance
   d. Gender
   e. Questioning

2. How important is the human brow in terms of subject recognition and signaling?
   a. Not important at all
   b. Very important, may be more important than the eyes
   c. May confuse the observer if the brows are absent due to plucking or disease
   d. Only important in men
   e. Only important in women

3. The attractive female eyebrow has all but one of the following features:
   a. Gentle convex shaped arch
   b. Thicker medially than laterally
   c. Change in direction of cilia orientation from medial to lateral
   d. Thinning of the lateral brow during middle age
   e. Growth of long spiky brow cilia from the central brow

4. The anagen duration of eyebrow follicles is approximately:
   a. 3-5 days
   b. 2-4 weeks
   c. 3 months
   d. 2 years

5. Finasteride is an effective treatment for androgenetic alopecia by inhibiting the enzyme:
   a. Alpha-1 antitrypsin
   b. 5α-reductase, type II
   c. Phenylalanine hydroxylase
   d. Thiopurine S-methyltransferase

6. Wnt signaling in hair follicle morphogenesis is mediated by which cytoplasmic protein:
   a. β-catenin
   b. Ectodysplasin
   c. Fibroblast growth factor
   d. Sonic hedgehog

7. Bimatoprost has been demonstrated to:
   a. Increase the length and thickness of eyebrow hair
   b. Increase the length and thickness of eyelash hair
   c. Improve periorbital rhytids
   d. Both a and b

8. Periorbital rejuvenation is most commonly performed by using injections of:
   a. Botulinum toxin type A
   b. Botulinum toxin type B
   c. Poly-L-lactic acid
   d. Hyaluronic acid

9. Methods of rejuvenating the periorbital area include laser, botulinum toxins, cosmeceuticals, fillers, and bimatoprost. Which has the highest rate of significant complications?
   a. Fractional non-ablative resurfacing
   b. Fractional ablative resurfacing
   c. Injections of botulinum toxins into the periorbital orbicularis oculi muscles
   d. Non-fractionated CO_2 laser resurfacing

Evaluation Form

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1 2 3 4 5

Enhanced my current knowledge base
1 2 3 4 5

Addressed my most pressing questions
1 2 3 4 5

Provided new ideas or information I expect to use
1 2 3 4 5

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