Cosmeceuticals for the Periorbital Region

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It is often said that the eyes are the windows into the soul, as they convey a form of expression that cannot be put into words. While time passes, and takes its toll on the body and the mind, the eyes remain true to self … ageless.

Similarly to the rest of the body, the periorbital region undergoes the effects of chronological aging and cellular senescence. This is associated with progressive failure of the highly regulated cellular mechanisms responsible for tissue health and renewal. Chronic sun exposure also leads to concomitant photo-aging, due to ultraviolet exposure from the sun [1, 2]. Although these processes affect the face as a whole, the thin nature of the peri-orbital skin makes this region even more prone to early signs of aging. The presence of superficial periorbital vessels and paucity of soft tissue also contribute to the potentially aged appearance.

A variety of treatment modalities can be used to address periorbital rejuvenation, ranging from minimally invasive and device based procedures, to surgical interventions [3]. Irrespective of the selected interventions, prevention, early treatment and long term maintenance with topical therapies is essential for optimal outcomes [4]. While topical therapies play an important role in treatment of pigment and texture, it is important that patients understand the extent of expected outcomes. Over time, skin laxity, fat loss and bone resorption may require more aggressive treatments.

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Skincare regimens also provide a synergistic effect to procedural interventions when paired correctly.

While skin may be the main target of topical interventions, the nearby eye lashes and eyebrows should also be treated as part of the aesthetic unit.

Products known as "eye creams" have oversaturated the market and are advertised as treatments for "dark circles", "puffiness" and wrinkles among others. In this chapter we will focus on the various substances and ingredients found in cosmeceuticals, which are known to provide actual benefit alone or in combination with other treatments. To be considered effective, these products must be able to penetrate the skin barrier, act locally, and provide effective and visible outcomes [5, 6].

Primary Assessment

Before initiating any treatment, be it topical or otherwise, a thorough survey of the patient's skin and general health are essential in guiding treatment (Box 9.1). This will allow treating physicians to better decide whether or not topical treatments will suffice or whether cosmeceuticals must be combined with other therapies.

Cutaneous and extra-cutaneous medical illnesses may present as altered pigment or texture of periorbital skin. Allergic shiners are one such example associated with atopic disease or asthma. Similarly, patients with dry eyes may tend to rub surrounding skin more frequently or vigorously, contributing to local skin irritation. Allergic history should also be noted as periorbital skin is sensitive and even mild topical treatments may not be tolerated. Knowledge of the underlying conditions can thus guide treatment but also set expectations.

Ask the patient about their main concern, previous treatments received, and their therapeutic expectations. Patients who understand their prescribed regimen are more likely to follow through with treatment plan and be satisfied with outcomes. Furthermore, patients' chief complaint can result from previous treatments. For example, superficial injection of under-eye fillers can result in bluish discoloration due to Tyndall effect.

Box 9.1 Primary Evaluation of the Periorbital Area Prior to Topical Treatment Initiation

General skin overview:

- Fitzpatrick skin phototype
- Presence of sun damage

Periorbital skin assessment:

- Skin texture
- Presence of swelling or puffiness
- Presence of dark circles
- Presence of wrinkles

Deep structure assessment:
1. Vascular show
2. Extent of volume loss
3. Extent of bone resorption

Other:
1. Hair distribution of lashes
2. Hair distribution of eyebrows

Box 9.2 Ingredients Commonly Found in Sunscreen

Common in chemical sunscreen:
- Zinc oxide∗
- Titanium dioxide∗
- Iron oxide
- Kaolin
- Ichthamol

Common in physical sunscreen:
- Oxybenzone
- Avobenzone
- Benzophenone
- Homosalate
- Octisalate
- Octocrylene
- Homosalate
- Octinoxate
- Methyl anthranilate
- Octyl methoxycinnamate

∗*Currently labeled in FDA's latest revision as "Generally Regarded As Safe and Effective"*

Other ingredients with insufficient safety data to date.

Sun Protection

Sun exposure contributed to extrinsic aging associated with wrinkling, collagen degradation, dryness and pigmentary changes. Ultraviolet A and B are the main culprits in this process. Daily and repeated application of sunblock helps mitigate sun damage (Table 9.1). Recent studies indicated that eyelids and the periorbital region are disproportionately missed during sunscreen application [7]. Further emphasis on overall skin coverage should be addressed by treating physician.

Chemical and physical sunscreens are both effective as long as they exceed a sun protective factor of 30 and are reapplied every few hours. The latter tend to be less irritant in nature, and may be better suited for sensitive periorbital skin (Box 9.2) [8].

Many makeup lines have created products that include sun protective ingredients however they may lack adequate efficacy. Alternately, tinted sunscreens may be a better option.

Table 9.1 Sunscreens and their properties

Product	Effect	Mechanism of action
Sunscreen		
Chemical sunscreen	• Prevention of photodamage • Prevention of post inflammatory pigmentary changes associated with energy-based treatments	Turn UV radiation into heat
Physical sunscreen		Disperse incoming radiation by means of reflection and absorption

Retinoids

These vitamin A derivatives have long been regarded as the mainstay treatment for maintenance of healthy youthful skin, acting both on intrinsic and extrinsic aging processes. Retinoids have proven clinical efficacy in treatment of irregularly pigmented skin as well as diminishing fine lines and wrinkles. Correction of skin dyschromia results from tyrosinase activity, the enzyme responsible for conversion of dopamine to melanin, with downstream effects on melanosome transfer. The textural effects are a result of simultaneous increased type I pro-collagen expression, and decreased collagenase activity, leading to dermal collagen synthesis [9]. There is also an observed hyaluronic acid deposition and compaction of the stratum corneum as well as increased epidermal mucin [10].

They are available in both prescription strength formulations such as tazarotene and tretinoin (retinoic acid), as well as over the counter products like retinol and retinaldehyde. While the former are more potent and lead to higher cutaneous concentrations, the latter are milder all while retaining clinical efficacy.

In spite of the excellent clinical efficacy of such products, they are notorious for producing dry, flaky and erythematous skin [11]. This is a particular concern when considering the sensitive periorbital area. Conjunctival irritation can also occur in case of direct contact with the eye. It is therefore preferable to use formulations that are less potent, or those containing emollients when treating the periorbital region. Progressively increasing the quantity and frequency of application can also be helpful to avoid skin irritation. Sun protection during treatment is crucial.

Antioxidants

Healthy skin has intrinsic capacity to repair damaged cells by means of an antioxidant defense system [12]. This includes scavenging and enzymatic processes that result in elimination of accumulated reactive oxygen species (ROS). ROS induce irregularities in skin cell DNA, lipids and proteins, leaving skin lax, discolored and with potential for cancerous growths. Antioxidants have the ability to increasing the minimal dose of UVB required to induce erythema of the skin, known as the Minimal Erythemal Dose (MED). By doing so, antioxidants reduce cellular damage, prevent sunburns, pigmentary irregularities and wrinkle formation (Table 9.2).

Table 9.2 Antioxidant properties

Antioxidants		
Vitamin C (L—ascorbic acid)	• Decreased sunburn potential • Decreased in wrinkles formation • Lightening of skin	• Electron donor • Neutralizer of free radicals • Suppression of NF-κβ • Inhibition of tyrosinase • Inhibition of enzymatic collagen degradation
Vitamin E (Tocopherols, Tocotrienols)	• Decreased sunburn potential • Decreased wrinkles formation • Decreased skin cancer potential	• Inhibition of elastin degradation by metalloproteinases
Ferulic acid	• Enhancement of photoprotection of vitamin C and E • Lengthening of skin	• Prevention of thymine dimer production • Prevention of keratinocyte apoptosis
Phloretin		• Prevention of lipid peroxidation • Prevention of metalloproteinases and elastase • Inhibit tyrosinase
Vitamin B3 (Niacinamide)	• Reduction in hyperpigmentation • Decreased wrinkle formation • Enhances skin barrier properties	• Enzyme cofactor • Inhibition of melanosome transfer from melanocyte to keratinocyte • Enhances lipid and protein in stratum corneum

Vitamin C is a water-soluble antioxidant with clinical proven efficacy. It also has anti-inflammatory and lightening benefits in addition to its role in collagen synthesis [13, 14]. Due to its hydrophilic nature, higher concentrations are necessary for adequate results. Lipid soluble formulations such as tetrahexyldecyl ascorbate have improved penetration capacity.

Vitamin E is a lipid soluble antioxidant with similar abilities in reduction of MED and wrinkle formation [15]. The main site of action is stratum corneum lipid bilayer and cell membrane. It has also been found to reduce development of skin cancers. α-tocopherol is the main active isomer. This product may be slightly irritating to some.

Ferulic acid and **Phloretin** are plant-based antioxidants with photoprotective effects [16]. When combined with vitamins C and E, they provide a stabilizing effect, enhancing photoprotection and vitamin penetration. Given that vitamins C and E are easily oxidized upon exposure to air, these combinations may be more suitable.

Vitamin B3 is a potent enzymatic cofactor with antioxidant properties and easy skin penetration capacity. Its stable nature allows it to easily be incorporated into topical therapies. In addition to wrinkle prevention and unification of pigment, this substance also enhances the skin's barrier capacity by reducing transepidermal water loss.

Alpha Hydroxy Acids (AHA)

This group of carboxylic acids includes lactic acid, glycolic acid, mandelic acid, citric acid, tartaric acid, malic acid and benzilic acid. They are commonly referred to as fruit acids. AHAs are incorporated into a number of skincare products

including exfoliants and chemical peels. By promoting separation of corneocytes at the junction between the stratum corneum and granulosum, treatment with AHAs leads to markedly increased epidermal thickness as well as enhanced glycosaminoglycan and collagen synthesis [6, 10]. This keratolytics effect is useful in photoaged skin with accumulated corneocytes.

Collagen Enhancing Products

In young skin, collagen production is able to keep up with normal breakdown, allowing the skin scaffold to remain firm. Over time, this process slows down, leading to increased skin laxity and wrinkle formation.

Up-regulated synthesis and down-regulated degradation of collagen by means of topical therapies can help enhance rejuvenation.

Topical **peptides** have been included in the armamentarium of anti-aging treatments. These are thought to act by multiple mechanisms including signaling cascades, carrier peptide action, enzyme inhibition, and neurotransmitter inhibition [17]. Collagen fragments and precursors have been studies both ex-vivo and in-vivo, showing potential anti-aging benefits. Inhibition of metalloproteinases has also been described. Pro-collagen products have lead to increased extracellular matrix protein production in fibroblast cultures. These effects allow adequate dermal remodeling to ensue. Neurotransmitter inhibiting peptides such as **argireline** may also diminish the appearance of wrinkles in a manner similar to that of injected neuromodulators. Clinical trials pertaining to the periorbital area specifically have been initiated and showed positive outcomes, however repeated and long-term application is necessary [18].

Cytokines and growth factors allow similar dermal fibroblast proliferation and tissue repair. Their role in stabilizing the dermo-epidermal junction, increasing dermal thickness and collagen production is well documented. As a result, products containing growth factors may potentially improve texture, pigment and wrinkle appearance. This includes Transforming Growth Factor (TGF), Vascular Endothelial Growth Factor (VEGF), hepatocyte growth factor, granulocyte colony stimulating factor, interleukins, epidermal growth factor, Platelet Derived Growth Factor (PDGF), Fibroblast Growth Factor (FGF), and insulin-like growth factor. These can be derived from human, animal or plant sources. In spite of the larger molecular structure, clinical studies showed positive outcomes in facial skin, with particularly superior results in the periorbital area [19, 20]. Histological data corroborates clinical findings associated with daily long-term topical treatment. Theoretical increased potential for growth or development of skin cancers, particularly with VEGF, warrants careful periodic revision of the literature.

Skin Lightening Agents

A common complain pertaining to the periorbital area includes hyperpigmentation. While the etiologies associated with this concern are out of the scope of this chapter, we will review some of the topical depigmenting options available [21].

It is noteworthy that the main etiology of hyperpigmentation should be established and treated. The mechanism of action of these agents mainly relies on inhibition of tyrosinase. **Hydroquinone** is a very effective and popular bleaching agent, which may be used in the periocular region. This is a potent treatment that can cause skin irritation acutely, and more serious dispigmentation with chronic use such as post-inflammatory hyperpigmentation, exogenous ochronosis, or leukomelanoderma en confetti. **Arbutin** is a plant extract with similar dose dependent tyrosinase action. It has been used in melisma treatments at a 3% concentration and may serve as an option for periocular hyperpigmentation. **Kojic acid** is a fungal derivative, which was shown to potentiate the action of hydroquinone when combined for treatment for hyperpigmentation. Further studies are needed to assess its efficacy in the periocular area. **Azaleic acid** is an alternative that has a better long-term safety profile [22]. This drug works by means of cytotoxic effect on melanocytes by interfering with DNA synthesis. It is more commonly used for general facial hyperpigmentation however may be a promising option in the periocular area.

Hydrating Products

Hyaluronic acid (HA) is a glycosaminoglycan with humectant properties, making it a popular component of over the counter anti-aging products. Although it plays an important water-binding role in the skin, the ability of hyaluronic acid to do so applied topically in unsure. The large molecular weight of HA would preclude it from penetrating the skin barrier. Nevertheless, some evidence of decreased wrinkle depth with topical application of low molecular weight HA was noted in the literature [23]. Similarly, **ceramides** serve as a lipid interface within the stratum corneum, allowing decreased transepidermal water loss. They are therefore often incorporated into eye creams for hydration purposes.

Hair Growth Products

Although the main focus of periocular rejuvenation remains skin health, long and full lashes provide a youthful and aesthetically pleasing appearance. **Bimatoprost** is a synthetic prostaglandin analog that was initially intended for treatment of glaucoma. Once daily topical application to the lash line was found to significantly thicken and lengthen eyelashes. This product comes in a 3% concentration form and is the only FDA approved lash enhancing treatment [24]. While the exact mechanism of action is unknown, bimatoprost is thought to increase the proportion of lash follicles in anagen as well as the duration of this phase. Off label use for eyebrows is common, as many clinical studies have found it to be an effective and safe treatment option in eyebrow hypotrichosis [25]. This product is generally regarded as safe with few irritant side effects to the eye. Due to reports of iris pigmentary changes, it is important to inform patients of the potentially permanent brown iris pigmentation.

Herbal, Plant Derived and Other Compounds

A variety of compounds are commonly found in commercially available products for periocular rejuvenation. While many of these are recurrent ingredients, their clinical efficacy is not well studied. We will briefly discuss them for completion however a recommendation for these products is unclear. Components of green tea have been described as potent antioxidants with photoprotective effects. Epicatechin-3-gallate and epigallocatechin-3-gallate in particular have demonstrated UV protection, down-regulation of deleterious NF-κβ expression and enzymatic degradation of collagen [26]. α-bisabolol, a compound found in chamomile as well as soy have exhibited some anti-oxidant and anti-inflammatory activity. Licorice root extracts have been described to provide lightening properties in addition to some anti-oxidant activity. Further clinical studies are needed for all these compounds before they can be recommended [6]. Similarly, caffeine has exhibited some anti-inflammatory effects. Nevertheless, it has been found to decrease collagen synthesis in cultured fibroblasts making it a potentially unfavorable ingredient for rejuvenation therapies. Peptides of palmitic acid (Palmitoyl tetrapeptide-7, Palmitoyl oligopeptide, Palmitoyl tripeptide-5) have been implicated in some dermal cellular mechanisms that may improve repair functions of the skin. They are incorportated into some products but their role for periorbital rejuvenation is unclear [5].

Role of Combination Treatments

While topical therapy may be an excellent cornerstone periorbital rejuvenation, a myriad of effective treatment options exist. When paired successfully, a baseline topical regime can prepare the skin for more invasive procedures, allowing optimal results [27]. While clinical studies are lacking, anecdotal findings have demonstrated that combining retinoids with certain non-ablative laser procedures results in earlier healing and re-epithelialization as well as superior and more lasting outcomes [28]. This consists of a pre-treatment phase with intensive treatment with topicals, and a post treatment phase with less abrasive products. Chemical peels are a common facial rejuvenation procedure. Adjunctive pre-treatments with AHAs and retinoids can begin thinning the stratum corneum prior to the procedure, allowing the peel to reach deeper in the skin. When combined with topical bleaching agents such as hydroquinone, the chemical peel may also allow deeper penetration of the topical agents, improving lightening capacity. Following procedures, topical humectants, such as HA and ceramides mentioned above, are commonly recommended to help with wound care.

Concluding Remarks

With the vast array of products and treatments available, physicians are able to provide their patients with many treatment options. While many of them have excellent clinical efficacy, it is important to know that not all products are suited for all

patients, and not all products are created equal, and even the best of products may not be sufficient to achieve desired results. Clinical judgment and a holistic approach should to be guide physicians to always offer what is best to each individual patient.

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