



VITAMIN A AND OSD: THE GOOD, THE BAD, AND THE UGLY



Understand the therapeutic benefits and potential adverse effects associated with products containing vitamin A derivatives.

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The significance of vitamins for maintaining ocular health cannot be overstated. Vitamin A, in particular, takes center stage in the context of dry eye disease (DED); however, its exact role in ocular surface disease (OSD) is a subject of controversy due to conflicting evidence of its benefits and potential harmful effects. This article delves into the intricate relationship between vitamin A and DED

and discusses various derivatives of vitamin A, including their mechanisms, therapeutic potential, and inherent risks.

VITAMIN A: THE BASIC FACTS

Vitamin A is a fat-soluble vitamin that supports immunity, growth and development, reproduction, gene transcription, cell differentiation and proliferation, epithelial cell health, and mucous membrane integrity.¹ Tissues requiring vitamin A, such as the liver and

the lacrimal gland, may store it as retinyl esters.^{2,3} Vitamin A deficiency remains a global issue, affecting approximately one-third of children worldwide and leading to blindness in 250,000 to 500,000 cases each year.^{4,5} However, in the United States, vitamin A deficiency affects only about 0.3% of the population, typically occurring in individuals with substance abuse or malabsorption issues.⁶ Vitamin A deficiency can result in the loss of goblet cells, increased epidermal keratinization, and squamous metaplasia of mucous membranes, including the conjunctiva,^{7,8} so it is crucial to consume a sufficient amount to support ocular health. Signs of vitamin A deficiency include night blindness, ocular surface dryness, dry skin, Bitot spots, frequent infections, and other skin problems.⁹ Dairy products, eggs, fish, meat, liver, leafy greens, carrots, and sweet potatoes are excellent sources of vitamin A.¹⁰

With respect to vision, vitamin A plays a pivotal role in transforming photons into electrical signals through a process known as phototransduction.¹¹ Vitamin A also exerts significant effects on goblet cells, corneal epithelial cells, tear film stability, and meibomian gland health.

VITAMIN A AND OSD

The relationship between vitamin A and OSD is complex. On one hand,

deficiency is detrimental to ocular surface health, and oral and topical supplementation has proven effective at improving the signs and symptoms of OSD.^{12,13} On the other hand, more potent derivatives can cause significant meibomian gland damage. Similarly, certain facial creams containing such potent derivatives, such as isotretinoin, may pose a risk to meibomian glands; patients should be advised not to use these products near their eyelids.¹⁴

As with any nutrient, moderation is key. It's essential to recognize that because vitamin A is a fat-soluble vitamin, toxicity is a possibility. Oral supplementation should generally be recommended only in cases of known deficiency, as toxicity is more common than deficiency in the United States.⁶ However, for patients suspected of mucin deficiency, meibomian gland hyperkeratinization, or aqueous deficiency, an ointment containing a mild vitamin A derivative may prove beneficial. It's worth noting that no evidence of ophthalmic ointments containing vitamin A and causing meibomian gland damage exists, but the theoretical risk is present.

VITAMIN A DERIVATIVES

Vitamin A exists in numerous forms, can be natural or synthetic, and is available by prescription and OTC (Figure 1). The more conversion steps a derivative requires before becoming biologically active, the less potent it

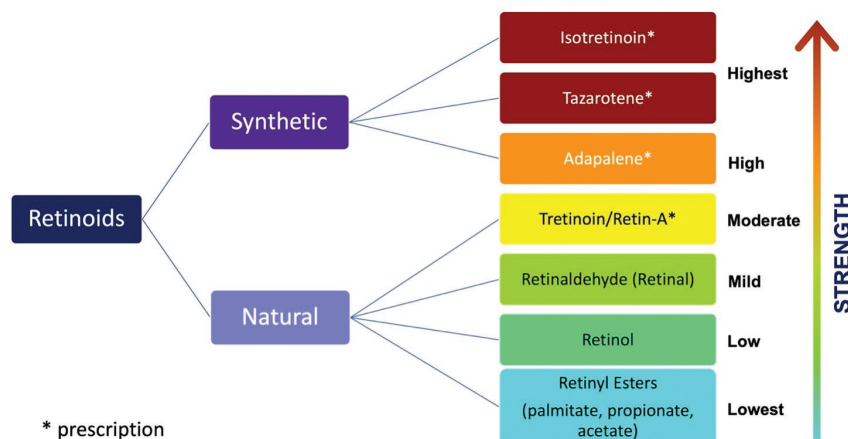


Figure 1. Common forms of vitamin A can be classified as natural or synthetic, prescription or OTC, and by strength (highest to lowest).

tends to be (see *Conversion Steps of Vitamin A Derivatives*). The reason for this is because each derivative is susceptible to degradation when exposed to air and sunlight and is therefore less likely to retain its active ingredient (eg, retinoic acid) over multiple conversion steps. Consequently, the specific derivative used in a product plays a critical role in determining its overall potency and risk profile.

THE GOOD

Vitamin A improves ocular surface health by promoting corneal epithelial cell health and wound healing, enhancing mucin production, and reducing keratinization of the ocular surface.

Promotion of Corneal Epithelial Cell Health and Wound Healing

Vitamin A promotes corneal cell healing via improved production of hyaluronic acid by corneal epithelial cells, which enhances the adhesion, extension, and migration of these cells, especially when affected by ocular surface desiccation.^{15,16} Topically administered retinol palmitate drops have been shown to accelerate the healing of corneal and conjunctival epithelial cells after injury,¹⁷ reduce corneal epithelial cell apoptosis,¹⁸ and improve signs and symptoms of dry eye.¹⁹

Enhanced Mucin Production

The mucous component of the tear film's mucoaqueous layer functions to bind the rest of the tear film to the ocular surface, thus contributing to the uniformity and stabilization of the tear film. A reduction in mucus can lead to tear film destabilization, resulting in corneal and conjunctival desiccation, which can further reduce mucin production by the goblet cells in the conjunctiva. Consequently, any decrease in mucin production can contribute to the onset and progression of DED.

In an animal model, serum vitamin A deficiency led to

AT A GLANCE

- ▶ Vitamin A promotes corneal healing, goblet cell function, tear film stability, and ocular surface health.
- ▶ Although vitamin A deficiency is detrimental to ocular surface health, more potent derivatives can cause significant meibomian gland damage.
- ▶ Eye care practitioners should ask patients about any history of oral isotretinoin use and skin care products containing vitamin A.

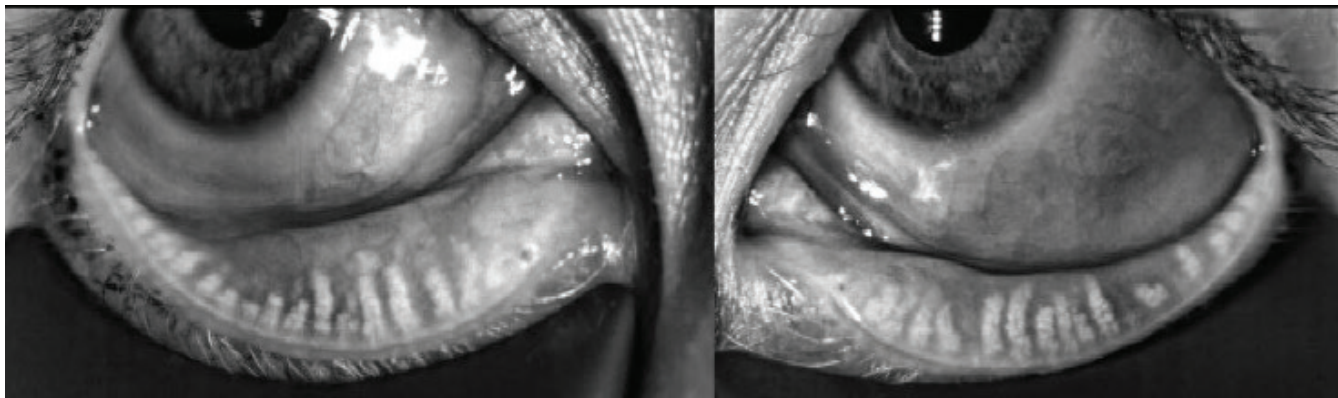


Figure 2. Meibography of a 28-year-old female patient with no preexisting OSD or risk factors who presented with severe dry eye symptoms after 8 months of oral isotretinoin therapy.

keratoconjunctivitis, characterized by superficial punctate keratitis and goblet cell loss. Interestingly, this condition was reversed within 3 weeks of treatment with retinol palmitate eye drops, despite serum vitamin A deficiency.²⁰ Moreover, topically administered retinol palmitate drops have been shown to increase the gene expression of mucin-producing cells in the cornea (*MUC4*) and goblet cells in the conjunctiva (*MUC5AC* and *MUC16*).²¹ This effect not only has the potential to enhance the function of conjunctival goblet cells, but may also reverse goblet cell loss, ultimately improving mucin production and tear film stability.^{22,23}

Reduction of Ocular Surface Hyperkeratinization

Lower levels of serum vitamin A have been associated with keratinization,^{24,25} contributing to hordeola and chalazia, especially in younger children whose meibomian gland ducts are thinner and, thus, more susceptible to obstruction.²⁶ Vitamin A deficiency also causes keratinization of the conjunctiva and cornea, which may be reversed with topical retinol palmitate eye drops.²⁷⁻²⁹

THE BAD

Understanding the potential negative effects of vitamin A requires a closer examination of specific derivatives. Dermatology frequently

employs vitamin A-based products to unclog pores, stimulate collagen production, and enhance collagen density.³⁰ The active ingredient that helps to counter aging and alleviate acne vulgaris is retinoic acid, which, in the case of aging, binds to retinoic acid receptors on the outer membrane of cells. In the context of acne, retinoic acid works by binding to sebocyte receptors and reducing sebum production.

Because meibomian glands function as specialized sebaceous glands in the eyelids, concerns arise for eye care providers. Any product that may inhibit meibum secretion could result in ocular issues, ranging from mild dryness to severe meibomian gland atrophy and associated ocular surface desiccation. Consequently, eye care practitioners should inquire about the use of skin care products containing vitamin A derivatives and consider cautioning against their periocular application, particularly with the use of more potent derivatives. In general, the term retinoids typically refers to stronger forms, while retinol and retinyl esters are associated with less potent OTC preparations.

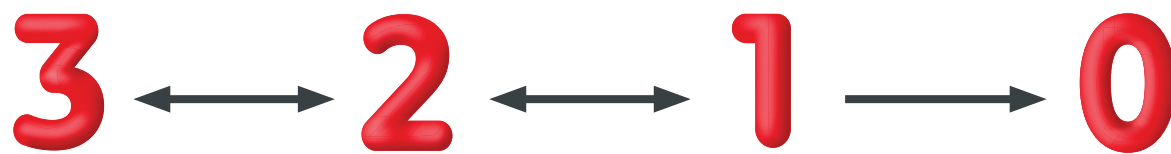
Additional in vivo studies are necessary to better understand the periocular application of vitamin A products and their effects on meibomian glands; however, eye care professionals should be aware of the potential risk to the ocular surface.

THE UGLY

Oral isotretinoin, also known as a 13 cis-retinoic acid, is prescribed to treat recalcitrant acne vulgaris by aggressively mitigating sebaceous gland secretions through sebaceous gland atrophy, thereby reducing sebum secretions by up to 90% within 6 weeks.³¹ However, the destruction of sebaceous glands is not relegated to the face; it also affects the meibomian glands. Isotretinoin has been shown to cause severe meibomian gland keratinization, acinar cell degeneration, periductal fibrosis, glandular atrophy, inhibited cell proliferation, epithelial cell death, altered gene expression, increased proinflammatory mediators, increased eyelid bacterial flora, conjunctival goblet cell toxicity, and eyelid margin telangiectasia.^{32,33} Such anatomic disruptions are associated with reduced tear breakup time, tear film hyperosmolarity, increased corneal staining, reduced goblet cell secretions, and severe DED symptoms.^{33,34} Although symptoms may improve after discontinuing isotretinoin, the morphologic changes to the meibomian glands are generally considered irreversible. Similarly, topical isotretinoin worsens signs and symptoms of DED, yet these changes are believed to be reversible.¹⁴

Further research is needed to better understand the effects of specific topical forms of vitamin A applied to the eyes and periorbitally. Until then, clinicians must rely on their clinical judgement and experience when

Conversion Steps of Vitamin A Derivatives



Retinyl Esters

Retinyl esters serve as a storage form of vitamin A and are found in the human body and animal tissues.¹ They become retinol in the gastrointestinal system.

Retinol

Retinol is more potent than retinyl esters, is naturally present in many foods, and is a popular ingredient in skin care products, known for its anti-aging and skin renewal benefits.

Retinaldehyde

Retinaldehyde, or retinal, is only one conversion step away from retinoic acid. Some skin care products incorporate this derivative to promote collagen production and reduce signs of aging.

Retinoic Acid

Retinoic acid, or tretinoin, the biologically active form of vitamin A, is used for treating various skin conditions, including acne and wrinkles, due to its effects on gene expression to stimulate skin cell turnover.

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discussing such products with patients. Although caution should be exercised with potent forms of vitamin A, it is generally safe to advise patients that a well-balanced diet rich in vitamin A can positively affect the health of their ocular surface.

STRIKE A BALANCE

The evidence shows that deficiency damages the ocular surface and meibomian glands and that oral supplementation in such cases is beneficial. We also know that administration of topical vitamin A is beneficial to the cornea and conjunctiva, but that stronger derivatives likely induce damage to the meibomian glands. What remains unclear is exactly what strength of vitamin A derivatives leads to reduced meibomian gland function when used orally or periorbitally. ■

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