Cosmesceutical Vitamins

Patrick Bitter, MD

The following potential conflict of interest relationships are germane to my presentation.

Speaker’s Bureau: Sciton Laser

Cosmeceutical Actives: Vitamins

Patrick Bitter, MD

- Scientific evidence shows that certain vitamins are useful in skin care
  - Prevention of photoaging and chronological skin aging
  - Topical and systemic treatment of photoaging and chronological skin aging
  - Management of acne vulgaris
Vitamins & Their Derivatives in Skin Care

- Vitamin A
  - Normalize keratinization
  - Downregulate sebum production in acne
  - Treat photodamage, striae, and cellulite
- Vitamin D (and analogs)
  - Downregulate cutaneous immune system
  - Downregulate epithelial proliferation and promote differentiation


Vitamins and Their Derivatives in Skin Care

- Vitamin C
  - Antioxidant
  - Regulates collagen synthesis (transcription and posttranslation)
  - Photoprotection (in combination with vitamin E)
- Vitamin E
  - Membrane antioxidant
  - Protects against oxidative damage
  - Photoprotection (in combination with vitamin C)

Vitamin A
**Vitamin A**

- Consist of natural and synthetic derivatives of Vitamin A
- Prescription retinoids
  - Retinoic acid
  - Synthetic naphthalene derivatives
    - Adapalene
    - Tazarotene
    - Bexarotene

**Vitamin A**

- Topical cosmeceutical retinoids
  - Retinyl esters
  - Retinol
  - Retinaldehyde
  - Oxoretinoids

**Retinoid Metabolism in Skin**

- Retinol is oxidized into retinaldehyde
- Retinaldehyde is oxidized into retinoic acid (biologically active form or vitamin A)

Retinoid Penetration

- Retinoids are lipophilic molecules that penetrate epidermis.
- Penetration of retinol and retinaldehyde investigated in vivo by measuring levels of skin enzyme cytochrome P-450-dependent RA 4-hydroxylase (CP450-RAH) with showing significant penetration and metabolism of retinol and retinaldehyde.
- Threshold concentration for adequate penetration and metabolism of retinaldehyde and retinol into retinoic acid is 0.025%.

Retinoid Metabolism Study

- Metabolism of retinol, retinaldehyde, and retinoic acid was studied using in vitro human skin and dermal fibroblasts.
- Radiolabeled retinol and retinaldehyde applied to skin biopsies or to cultured media of fibroblasts.
- Analyses demonstrated gradient distribution of retinoids within skin and metabolism of retinol and retinaldehyde to retinoic acid.

Biologic Properties of Retinoids

- Antioxidant activity via free radical quenching.
- Increased fibroblast proliferation.
- Modulation of cellular differentiation and proliferation.
- Increased collagen and hyaluronate.
- Decreased metalloproteinase-mediated extracellular degradation.

©Sharon McQuillan, MD. All rights reserved.
Retinoid Mechanism of Action

- Fine lines and wrinkles
- Hyperpigmentation
- Skin roughness

Retinoids: Fine Lines & Wrinkles

- Retinoic acid reduces fine lines and wrinkles by increasing capacity of epidermis to hold water through stimulation of glycosaminoglycan (GAG) synthesis
- Also stimulates collagen synthesis by increasing transforming growth factor β (TGF-β) and procollagen
- May retard or prevent further dermal matrix degradation by inhibiting enzymes that break down collagen and prevent oxidative stress

Retinoids: Hyperpigmentation

- Retinoic acid thought to reduce pigmentation by enhancing epidermal cell turnover
- Enhancing epidermal cell turnover decreases contact time between keratinocytes and melanocytes and promoted rapid loss of pigment via epidermopoiesis

**Retinoids: Skin Roughness**

- Reduces skin roughness by modulating expression of genes involved in cellular differentiation and proliferation, promoting epidermal cell turnover
- Believed to be mediated via binding to retinoic acid receptors (RAR) and subsequent binding of these complexes to specific genes affecting gene transcription

**Retinoids**

- Negative effects of topical retinoids
  - Skin irritation
  - Tetragenic effects
- Retinoic acid precursors used widely in skin care industry to minimize these effects and still effectively treat photodamaged skin

**Retinol**

- Naturally occurring form of Vitamin A
- Precursor to retinoic acid
- Derived by hydrolysis of beta-carotene
- Used for topical treatment of photodamage and acne
- Activity substantially increased when applied under occlusion
Retinaldehyde

- Formed by oxidation of alcohol group of retinol
- Studies show retinaldehyde can successfully treat rosacea with better patient toleration than retinoic acid

Retinyl Esters: Retinyl Propionate and Retinyl Palmitate

- Store vitamin A in lipids
- Retinyl propionate shown to elicit retinoid effects in treating photodamage with less irritation
- Studies suggest retinyl palmitate has weak activity

Retinyl Propionate Results
Tretinoin

• Trans-retinoic acid
• Used in treatment of acne and photoaging


Tretinoin

• Role of tretinoin first described by Kligman
  – Demonstrated significant effects on photodamaged skin
  – Reversal of epidermal atrophy, dysplasia and atypia
  – Eradication of microscopic actinic keratoses
  – Uniform dispersing of melanin
  – New collagen formation

Tretinoin

• Formal clinical trials have proven tretinoin reverses photoaging at a dermal and epidermal level
• Epidermal effects
  – Epidermal thinning
  – Reduction in corneocyte adhesion
  – Decreased melanin production
  – Increased Langerhans cell production
Tretinoin

- Dermal effects
  - Increased collagen production
  - Increased angiogenesis
  - Decreased collagenase
  - Decreased glycosaminoglycans


Topical Retinol Study

- Comparative, investigator-blinded, split-face study
- Hydroquinone 4%/retinol 0.3% compared with tretinoin 0.05% among 41 women with mild to moderate photodamage
- Both preparations associated with superior improvement in pigment parameters


Topical Retinol Study

- Randomized, double-blind, vehicle-controlled trial in elderly patients with naturally aged skin
- Mean age=87 years
- Retinol 0.4% lotion or vehicle control applied to patients’ forearm 3 times/week for 24 weeks
- Retinol treated skin associated with significant improvement in fine wrinkle scores compared to baseline
- Topical retinol associated with increase in GAG expression and procollagen I

**Topical Retinoic Studies**

- 0.05% retinaldehyde vs. 0.05% retinoic acid vs. vehicle in 125 patients over 18 weeks in non-doubled-blind and non-randomized study.
- Retinaldehyde can also produce significant clinical improvement in fine lines and deep wrinkles.


**Topical Retinoid Studies**

- 0.4% retinol vs. vehicle in randomized, double-blind, vehicle-controlled, left and right arm comparison study in 36 elderly patients 3 times per week for 24 weeks.
- Clinically, retinol improved fine wrinkling with significance (p<0.001).
- Histologically, biopsies showed retinol significantly increased GAG expression and procollagen.


**Vitamin E**
**Vitamin E**

- Functions as major lipophilic antioxidant in plasma, membranes, tissues
- Refers to eight molecules
  - Four tocopherols
  - Four tocotrienols
- α-tocopherol most abundant form in body

**Vitamin E**

- Most important lipid-soluble antioxidant found in membranes
- Two basic forms
  - Tocopherols
  - Tocotrienols

**Vitamin E**

- Scavenges lipid peroxyl radicals
- Predominant physiologic antioxidants of skin barrier
- May enhance photoprotective properties of sunscreen
- Clinical studies show that chronic skin conditions such as wrinkling and skin tumor incidence due to prolonged UV exposure are diminished by topical vitamin E
**Vitamin E**

- Topically applied vitamins C, E, and ferulic acid act synergistically to compound antioxidant and photoprotective properties
- Vitamin C regenerates active form of vitamin E
- Ferulic acid stabilizes vitamins C and E

---


---

**Vitamin E and Scars**

- Vitamin E used historically to minimize scar appearance
- 12 week double-blinded study comparing vitamin E to control
- Vitamin E did not improve cosmetic outcome of post surgical scars
- Caused contact dermatitis in 33% of treated subjects

**Vitamin E**

- Most frequently used cosmeceutical ingredients
- Lack of published data on dose-response studies regarding vitamin E
- Doses of 50 IU-1000 IU $\alpha$-tocopherol per day tolerated in humans with little to no side effects
- Clinical studies suggest that orally administered vitamin E improves facial hyperpigmentation


**Vitamin C**

- Water soluble, acidic, essential for life
- Essential for hydroxylation of precollagen, lysine
- Regenerates vitamin E and quenches free radicals
Vitamin C (Ascorbic Acid)
- Effective treatment for inflammatory dermatoses
- Anti-inflammatory and antioxidant properties
- Promotion of collagen synthesis
- Inhibition of collagen degradation
- Reduction of hyperpigmentation
- Acts to regenerate vitamin E from tocopheroxyl radical

Therapeutic Used for Vitamin C
- Photodamage
- Photoaging
- Hyperpigmentation
- Erythema

Vitamin C
- Normalizes histological changes of photodamage
- Skin levels depleted after UV exposure
- Three forms of vitamin C found in cosmeceuticals
  - L-ascorbic acid
  - Ascorbyl-6-palmitate
  - Magnesium ascorbyl phosphate (most stable)
Vitamin C Clinical Study

- Topical L-ascorbic acid shown to protect skin from UVB induced erythema and sunburn cell formation
  

Vitamin C Clinical Study

- 3 month, double blind vehicle
- N=19
- Split-face study 0.5 mL Cellex-C high potency serum 10%
- Photographs, periorbital optical profilometry, and patient self assessment
- 73.9% improvement in periorbital wrinkles
- 57.9% improvement in photographic assessment over control
- Patients reported 84.2% improvement over control
  
  Traikovich SS. Arch Otolaryngol Head Neck surg 1999: 125;1091.

Beneficial Effects of Topical Vitamin C in Photodamaged & Photoaged Skin

- Randomized, double-blind, placebo-controlled trial
- Topical vitamin C 5% cream used over 6 months vs. placebo
- Skin treated with vitamin C cream associated with significant improvement in physician and patient assessments
- Significant increase in skin density
- Decrease in skin wrinkles
- Histological evidence of elastic repair
  
**Vitamin C & E Synergistic Effects Study**
- L-ascorbic acid 15% and α-tocopherol 1% used either alone or in combination vs. vehicle control
- Individual ingredients resulted 2-fold increase antioxidant protection
- Combination produced 4-fold increase in antioxidant protection


---

**Vitamin C Study**
- Double-blind, split-face trial
- Topical solution containing 10% L-ascorbic acid and 7% tetrahexyloxyethyl ascorbate compared with control
- After 12 weeks, wrinkling and photodamage significantly reduced on cheeks, forehead, and perioral region on treated side of face.

**Vitamin C Study**

- In study of postmenopausal women, vitamin C increased pro-collagen mRNA and associated enzymes to bolster collagen synthesis

Nusgens BV et al. Topically applied vitamin C enhances mRNA level of collagen I and III, their processing enzymes and tissue inhibitor of matrix metalloproteinase in human

**Vitamin B3: Niacinamide**

- Precursor of cofactors niacinamide adenosine dinucleotide (NAD) and niacinamide adenosine dinucleotide phosphate (NADP)
- Cofactors and reduced forms (NADH and NADPH) serve as reduction-oxidation coenzymes in more than 40 cellular biochemical reactions
**Niacinamide Penetration**

- Studies demonstrate significant penetration into human skin
- Increased levels of NAD have been used as evidence of percutaneous penetration

**Vitamin B₃ - Niacinamide**

- Niacinamide increases epidermal turnover, improves barrier function, decreases photoaging, reduces sebum production
- Does not irritate skin

**Niacinamide: Mechanisms of Action**

- Antioxidant capacity
- Epidermal barrier function
- Erythema and blotchiness
- Skin yellowing
- Fine lines and wrinkles
- Hyperpigmentation
Antioxidant Capacity

- Increases antioxidant capacity of skin after topical application by increasing the reduced form NADPH, which has potential antioxidant properties.

Epidermal Barrier Function & Niacinamide

- Evidenced by reduced TEWL (transepidermal water loss) and increase in skin’s resistance to potential harmful topical agents.
- Proposed mechanisms of action:
  - Increased synthesis of ceramides via upregulation of serine palmitoyl transferase, the rate limiting enzyme in sphingolipid synthesis.
  - Stimulate keratinocyte differentiation by influencing keratin K1, which results in epidermal turnover.

Skin Yellowing & Niacinamide

- Yellowing of skin that occurs with aging may be result of glycation of proteins in skin (Maillard reaction).
- Maillard reaction – spontaneous oxidative reaction between protein and sugar resulting in cross-linked proteins that are yellow-brown in color (Amadori products) and accumulate in skin matrix components.
Skin Yellowing and Niacinamide

- NADH and NADPH are antioxidants and their levels are influenced by niacinamide, a possible effect of topical niacinamide is inhibition of oxidative processes, leading to the decrease of skin yellowing.

Niacinamide: Fine Lines & Wrinkles

- Multiple mechanisms may be involved in ability of niacinamide to reduce appearance of fine lines and wrinkles
- May have ability to increase dermal collagen and protein production
- As precursor of NAD/NADP, niacinamide stimulates collagen synthesis and keratin, filagrin, and involucrin
- Ability to reduce GAGs

Niacinamide and Erythema, Blotchiness

- Mechanism which improves redness/blotchiness may be related to improved skin barrier function
- Increasing barrier function may result in less irritation when skin encounters environmental insults resulting in less redness
- Theory has not been substantiated
Niacinamide and Hyperpigmentation

- Reduces melanosome transfer from melanocytes to surrounding keratinocytes
- 5% niacinamide moisturizer provided 35-68% inhibition of melanosome transfer from melanocytes to keratinocytes


Potential Clinical Use of Niacinamide

- Dry skin
- Acne
- Photoaging
- Blistering disorders
- Pigment disorders
- Wound healing

Niacinamide Clinical Studies

- Randomized, double-blind studies of Japanese and white patients
- Topical niacinamide 2% produced significant effects on sebum excretion and sebum levels in Japanese patients
- Significant reduction in facial shine, oiliness, and overall skin appearance in white patients

Niacinamide Clinical Studies

- 5% topical nicotinic acid derivative applied for 12 weeks vs. placebo in patients with photodamage
- 25% increase in skin NAD levels
- 70% increase in epidermal thickness


Niacinamide Results

Niacinamide Studies

- 3.5% niacinamide cream was compared with placebo for 4 weeks and demonstrated 14.8% reduction in skin roughness (p = 0.05)

Tano O et al. Nicotinamide increases biosynthesis of ceramides as well as other stratum corneum lipids to improve epidermal permeability. 2000.
Niacinamide Studies

- Randomized, double-blind, split-face, placebo-controlled clinical trial
- 50 white females applied 5% niacinamide and vehicle twice daily for 12 weeks
- Results showed significant improvement in fine lines, wrinkles, hyperpigmentation, redness, yellowing, skin elasticity (p>0.05)


Vitamin B₅ - Panthenol

- Promotes fibroblast synthesis, epidermal re-epithelialization, increased skin lipid synthesis
- Skin penetration enhancement
- Used topically to treat wounds, bruises, scars, pressure and dermal ulcers, dermatoses

©Sharon McQuillan, MD. All rights reserved.
Panthenol

• Addition of panthenol to topical formulations should reduce effects of:
  – Redness
  – Burning
  – Tingling
  – Stinging
  – Itching


Effects of Panthenol

• Hydration: moisturizes stratum corneum, improves elasticity
• Barrier functions: protects against irritation by improving and repairing skin barrier functions

Panthenol Studies

• Topical pretreatment with panthenol observed to increase skin’s resistance to visible irritation upon exposure to sodium lauryl sulfate (SLS)
• Topical panthenol can be incorporated into skin care formulations to reduce negative effects of product irritation
Prevention of SLS-induced Erythema by Topical Panthenol (0-6 scale)

<table>
<thead>
<tr>
<th>Time post SLS treatment</th>
<th>Erythema score</th>
<th>Erythema score panthenol</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 days</td>
<td>4.0</td>
<td>2.4</td>
</tr>
<tr>
<td>3 days</td>
<td>3.4</td>
<td>1.7</td>
</tr>
<tr>
<td>4 days</td>
<td>2.7</td>
<td>1.4</td>
</tr>
</tbody>
</table>

Reduction in Negative Kinesthetic Effects of Formulation Containing Panthenol vs. Control

<table>
<thead>
<tr>
<th>Visible/Kinesthetic Attribute</th>
<th>Reduction by Panthenol (0-6 scale)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Redness</td>
<td>-1.4</td>
</tr>
<tr>
<td>Burning</td>
<td>-2.4</td>
</tr>
<tr>
<td>Tingling</td>
<td>-5.7</td>
</tr>
<tr>
<td>Itching</td>
<td>-4.9</td>
</tr>
<tr>
<td>Stinging</td>
<td>-4.9</td>
</tr>
<tr>
<td>Warming</td>
<td>-5.7</td>
</tr>
</tbody>
</table>


Vitamin D
Vitamin D

- Several vitamin D compounds and many synthetic variations
- Active vitamin: 1,25-dihydroxyvitamin D₃
- Dehydrocholesterol (provitamin D) cosmetically used ingredient which is converted into active vitamin D upon UV exposure

As a result of effects of vitamin D on epidermal growth and differentiation, there has been discussion of skin barrier and photodamage mitigation activities
- Topical vitamin D analogs used successfully in treatment of psoriasis thought to regulate cutaneous immune system and downregulate epithelial proliferation and promote differentiation

Vitamin K
**Vitamin K**

- Phylloquinone: lipid soluble vitamin K
- Synthetic form (vitamin K3)- menadione
- Vitamin K compounds function in blood clotting

**Vitamin K Clinical Studies**

- Blinded clinical trial with split face method compared vitamin K with placebo in bruising severity
- Another study compared vitamin K plus vitamin A with placebo in similar trial methods
- Each study consisted of 20 subjects that demonstrated decreased bruising, frequency, and severity when applied prior to and after pulsed dye laser treatment
- Both vitamin K products produced statistically significant results over placebo