Hydroxy Acids

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Abstract

Hydroxy acids (HAs) represent useful substances for skin care and chemical peelings and have been used typically in concentrations ranging from 2% to 70%, depending on the indication, pH, formulation, and application schedule. The higher the concentration and the lower the pH of the product, the greater the exfoliative, epidermolytic, and even toxic and corrosive action.

The most widely used hydroxy acids are glycolic, mandelic, and salicylic acids. Recently, other substances like β-lipohydroxy acids (BLHAs) and gluconolactone have been developed in order to enhance efficacy and diminish irritation.

The main effects of hydroxy acids in the skin are hydration, exfoliation, acceleration of collagen synthesis and modulation of matrix degradation, epidermal turnover regulation, inhibition of tyrosinase activity, and free radical neutralization.

The uses of hydroxy acids include the treatment of dry skin, hyperkeratinization, acne, rosacea and sensitive skin, hyperpigmentation, wrinkles, and photoaging, with a high tolerance and good safety profile.

Keywords

Hydroxy acids • α-Hydroxy acids • AHA • Salicylic acid • Glycolic acid • Bionic acid • Polyhydroxy acid • β-Hydroxy acids • β-Lipohydroxy acid • Chemical peels • Mandelic acid • Gluconolactone • Photoaging • Hyperpigmentation • Acne

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Introduction

In the mid-1970s, Van Scott and Yu found that hydroxy acids (HAs) with a hydroxyl group at the α- or β-position, when applied topically, had a very specific effect on hyperkeratinization. This effect was clinically expressed by an initial abrupt detachment of the hyperkeratotic stratum corneum at its innermost level, stratum compactum, distal to the stratum granulosum, providing beneficial effects for ichthyosis, dry skin, keratoses and warts, and follicular hyperkeratosis, including that occurring in acne (Van Scott and Yu 1974, 1984).

Since then, HAs transformed skin care and have been used typically in concentrations ranging from 2% to 70%. In low concentrations (4–10%), the HAs are ubiquitous components of nonprescription creams and lotions that are promoted as being effective for ameliorating skin aging. In high concentrations (>20%), these preparations are used as chemical "peels" to treat calluses, keratoses, acne, psoriasis, and photoaging (Kornhauser et al. 2010).

Sustained applications of α-HAs (AHAs) and β-HAs (BHAs) result in plumping of the skin, and, although some epidermal thickening occurs, dermal thickening is correlated with biosynthesis of glycosaminoglycans (GAGs), collagen, and improved quality of elastic fibers. These dermal changes improve fine lines and wrinkles (Ditre et al. 1996).

α-Hydroxy Acids (AHAs)

The AHAs are organic carboxylic acids with one hydroxyl group attached to the α-position of the carboxyl group. The hydroxyl group in the AHA is neutral, and only the carboxyl group provides an acidic property. Many AHAs are present in foods and fruits and, therefore, are called fruit acids. Naturally, it occurs in grapes, sugarcane juice, and sugar beets. It is strongly hygroscopic, so it has to be kept in closed bottles.

Glycolic acid (hydroxyacetic acid) is the smallest and simplest representative of AHA and also the most widely used in skin care.

Lactic acid, with optimal biologic activity in its L-form, is the next smallest molecule and is also used in various topical formulations to exfoliate the skin and also to provide antiaging properties (Kornhauser et al. 2010). It ameliorates the skin by increasing the levels of stratum corneum ceramides and glycosaminoglycans (Piérard et al. 1999).

Some AHAs contain a phenyl group as a side-chain substituent. This changes the solubility profile of AHA, providing increase lipophilicity over conventional water-soluble AHAs, and can be used to target oily and acne-prone skin. Examples include mandelic acid (phenyl glycolic acid) and benzilic acid (diphenyl glycolic acid) (Green et al. 2009). The addition of mandelic acid and benzilic acid to 0.5% salicylic acid has been shown to provide significant oil-reducing properties and a favorable tolerability profile while offering a concentration of salicylic acid that can be used nearly worldwide (Green 2005).

In 1998, the Cosmetic Ingredient Review (CIR) Expert Panel recommended limitations on the concentration of AHAs (<10%) and the pH (at or above 3.5) of cosmetic products containing AHAs. In addition, these products should be formulated to avoid sun sensitivity, and consumers should be advised to use daily sun protection (Kornhauser et al. 2010).

The chemical structure, acidity, and source of the different AHAs are presented in Table 1.

Mechanism of Action

An important epidermal effect is the increase of water holding capacity due to AHA application along with an increase of skin hydration and skin turgor. Besides, AHAs induce desquamation, plasticization, and normalization of epidermal differentiation by interfering with intercellular ionic bonding, thereby reducing corneocyte cohesion and thus inducing keratolysis. The higher the concentration of the acid and the lower the pH of the product, the faster keratolysis is induced and may even lead to epidermolysis (Babilas et al. 2012).

Table 1 AHAs – chemical structure, acidity, and source (Babilas et al. 2012)

Name	Molecular formation	Acidity (pKa)	Natural source
Lactic acid	$C_2H_6O_3$	3.86	Fermented milk products
Citric acid	$C_6H_8O_7$	3.09	Citrus fruits
Mandelic acid	$C_8H_8O_3$	3.41	Bitter almonds
Glycolic acid	$C_2H_4O_3$	3.83	Sugarcane
Tartaric acid	$C_4H_6O_6$	3.22	Fermented grapes
Ascorbic acid	$C_6H_8O_6$	4.10	Fruits
Malic acid	$C_4H_6O_5$	3.40	Apples

Evidence has been published on the AHA's ability to increase dermal and epidermal glycosaminoglycans (GAGs) (Ditre et al. 1996; Bernstein et al. 1997) and to prevent both epidermal and dermal atrophy resulting from long-term topical corticosteroid use (Lavker et al. 1992).

In vitro studies using cultured human skin fibroblasts have shown a dose-dependent increase of cell proliferation and collagen production (Kim and Won 1998).

Other effects documented in literature are increased synthesis of GAG, increased dermal thickness, fibroblast proliferation, and induction of factor XIIIa transglutaminase (Grossman and Matarasso 2002).

Okano et al. conducted a study that investigated the effects of glycolic acid on the dermal matrix metabolism of keratinocytes and fibroblasts using in vitro and ex vivo (human skin biopsies) systems. That study showed that glycolic acid not only directly accelerates collagen synthesis by fibroblasts but also modulates matrix degradation and collagen synthesis through keratinocyte-released cytokines. Their experiments confirmed that IL-1a is one of the primary mediators regulating matrix degradation that are released from keratinocytes after glycolic acid treatment. On the basis of their findings, the authors suggest that glycolic acid contributes to the recovery of photodamaged skin through various pathways, depending on the skin cell type (Okano et al. 2003).

Safety Profile

Usually, a daily-based application by patients themselves using a concentration up to 20% is tolerated very well and evokes only a minor rate of side effects. The potential side effects are mild-to-moderate skin irritation, stinging or burning sensation, pain, and erythema.

If a higher concentration is used, i.e., office-based treatments, the side effects become more frequent. The possible adverse events include pain, blistering, purple or crusting, erythema, hypopigmentation, hyperpigmentation, atrophy, ulceration, scarring, hypertrophic scarring or keloid formation, and infection.

The most frequent side effect following AHA's peeling is a persistent erythema. While burning sensation probably lasts only for hours in case of a mild peeling, it may last for months if a deep peeling is applied (Babilas et al. 2012).

B-Hydroxy Acids (BHAs)

The BHAs are organic carboxylic acids having one hydroxyl group attached to the β-position of the carboxyl group. The hydroxyl group in the BHA is neutral in nature, and the carboxyl group provides the acidic property (Green et al. 2009).

Malic acid and citric acid are prominent representatives in this category.

Citric acid is widely used in topical formulations as an antioxidant and pH adjustor, and its antiaging benefits are well established (Bernstein et al. 1997).

Salicylic Acid (SA)

In cosmetic and dermatologic literature, salicylic acid (SA) is often described as a BHA, but that classification is incorrect (Yu and Van Scott

1997.) In SA, both hydroxyl and carboxyl groups are directly attached to an aromatic benzene ring, and both exhibit acidic properties. In contrast, the hydroxyl groups in AHAs, BHAs, and PHAs are neutral under the conditions used in clinical and cosmetic settings. On the basis of knowledge to date, SA does not function physiologically or therapeutically as a BHA. Furthermore, AHAs are soluble in water and SA is not.

SA is widely used in cosmetic formulations (concentrations 2–4%) and also therapeutically as a keratolytic agent to treat skin conditions such as calluses, keratosis, acne, and photoaging. It is especially useful in subjects with oily skin (Kornhauser et al. 2010.)

Several experimental and clinical studies have found that topically applied SA is photoprotective, having a pronounced filter effect when applied prior to UVB exposure (Kornhauser et al. 2010).

The antibacterial action of SA has been known for many decades. A study indicates that SA acts at the level of transcription to downregulate the production of fibrinogen, fibronectin, and α-hemolysin virulence factors necessary for bacterial replication in host tissues (Herrmannn 2003).

SA at high concentrations (30%) induces hyperplasia of the epidermis and improves the dispersion of melanosomes, which makes it useful in treating hyperpigmentation (Klingman and Klingman 1998).

It is important to remember that toxicity and hepatic injury are possible side effects of SA. It should be applied only to small surface areas and for limited periods of time.

β-Lipohydroxy Acid (BLHA)

A C-8 derivative of SA known as β-lipohydroxy acid (BLHA), developed in the late 1980s, has been proposed as an exfoliant and as a treatment for photoaged skin and acne. BLHA has an eight-carbon fatty chain linked to the benzene ring making it more lipophilic than SA.

BLHA was shown to have a good safety profile with lower irritation when compared to glycolic acid (GA). It has antibacterial effects, which are ideal for the treatment of acne (Kornhauser et al. 2010). It also has a marked affinity for the comedos. After a 1-month treatment with 2% BLHA, there was a decrease of the number of follicular casts compared to placebo ($p < 0.01$) (Piérard et al. 1999).

Creams containing 2% SA or BLHA were found to enhance the shedding of corneocytes and reduce the thickness of the stratum corneum. The penetration of SA and the AHAs is relatively rapid, and consequently the breakdown of central corneosomes occurs throughout the stratum corneum. BLHA, on the other hand, appears to have a more restricted action due probably to its lipophilic nature and its relatively slower penetration. This molecule causes the desmosome to fracture at the stratum disjunctum/compactum interface, where it produces relatively clean breaks and therefore more closely mimics the physiologic process.

In clinical trials using 1% BLHA, volunteers reported significant improvement in softness, tonicity, and comfort of the skin (Saint-Léger et al. 2007). In isolated human skin, 1.5% BLHA has been found to significantly increase cell renewal versus control versus 5% SA. An order of potency for this response has been established: 0.05% all-trans-retinoic acid >2% BLHA >> 10% GA (Piérard et al. 1999).

BLHA (1–5%) dose-dependently stimulated collagen formation in a human reconstructed skin model and increased filaggrin content in human skin biopsies (Piérard et al. 1999).

When applied 3x/day, a low concentration (0.3%) of BLHA was found to slightly but significantly reduce skin pigmentation induced by daily exposure to sub-erythemal UV dose. This protective effect can be explained by its antioxidant properties (Piérard et al. 1999).

Table 2 presents a comparison of the effects of retinoic, glycolic, and β-lipohydroxy acids.

Polyhydroxy Acids (PHAs)

A new generation of AHAs, called polyhydroxy acids (PHAs), provides similar effects, but with less irritation response. The PHAs are organic carboxylic acids with two or more hydroxyl groups in the molecule attached to carbon atoms

Table 2 Comparison of retinoic, glycolic, and β-lipohydroxy acids (Piérard et al. 1999)

	Retinoic acid	Glycolic acid	BLHA
Pigmentation – epidermal pigmentation	↓	↓	↓
Pigmentation – melanosome cluster frequency	↓	-	↓
Exfoliation – shedding of corneocytes	↑↑	↑	↑↑
Exfoliation – thickness of the stratum corneum	↓	↓	↓
Exfoliation – smoothness of the skin	↓	↓	↓
Acne – comedolytic activity	Yes	No	Yes
Acne – antibacterial activity	No	-	Yes

of an aliphatic of alicyclic chain. All the hydroxyl groups in the PHA are neutral, and only the carboxyl group provides its acidity (Green et al. 2009).

Gluconolactone is the most commercialized PHA in skin care products, because it is readily available and delivers the antiaging benefits of HAs, in addition to strengthening skin barrier function and being a gentle, moisturizing, antioxidant/chelating substance.

An in vitro cutaneous model of photoaging demonstrated that gluconolactone protects – up to 50% – against ultraviolet (UV) radiation. As the UV absorption of gluconolactone is low, these findings were attributed to the ability of gluconolactone to chelate oxidation-promoting metals and trap free radicals (Bernstein et al. 2004). Gluconolactone can be formulated with oxidative drugs, such as benzoyl peroxide, to help reduce irritation potential and erythema cause by the oxidative drug (Kakita and Green 2006).

Gluconolactone has demonstrated efficacy for improving skin moisturization, fine lines and wrinkles, skin laxity, uneven skin tone, roughness, and pore size (Green et al. 2001).

Bionic Acids (BAs)

The BAs are chemically classified as aldobionic acids. They consist of one carbohydrate monomer chemically linked to analdonic acid and lactobionic acid; maltobionic acid and cellobionic acid are some examples.

Because of the multiple hydroxyl groups, lactobionic acid is a strong humectant and more effective than regular AHAs, and it could be presumed that it increases the synthesis of GAGs in the skin, due to the presence of D-galactose, a naturally occurring sugar needed for the GAG synthesis and skin metabolite, attached to the polyhydroxy acid structure (Tasic-Kostov et al. 2010).

Although the BAs are larger molecules than the traditional AHAs, they are small enough to penetrate the skin at approximately 358 Da, and their pKa is roughly equivalent to smaller AHA molecules.

BAs are hygroscopic materials that readily attract and retain water, forming a gel matrix when their aqueous solution is evaporated at room temperature. Formation of a gel matrix may add protective and soothing effects for inflamed skin. Indeed, formulations containing BA are well tolerated and help calm the skin when applied after cosmetic procedures that weaken the skin's barrier, including superficial HA peels and microdermabrasion (Green et al. 2009).

Green performed a study of the effects of lactobionic acid-containing products and revealed improvement in all photoaging and texture parameters on exposed skin, with no signs of intolerance (Green 2000).

Lactobionic acid also functions as an inhibitor of the matrix metalloproteinase (MMP) enzymes. The excessive activity of MMPs occurs with age and sun exposure, contributing to wrinkle formation, skin laxity, and visible telangiectasia. The use of BAs to inhibit MMPs may provide a significant benefit in the prevention of photodamage (Green et al. 2009).

Tasic-Kostov et al. conducted a study to assess the safety and efficacy of lactobionic acid as compared to glycolic acid and found out that lactobionic acid resulted in improved skin benefits as compared with corresponding glycolic acid

Table 3 Safety and mechanism of action of hydroxy acids (Kornhauser et al. 2010)

Types of HAs	Safety evaluation	Mechanism of biological action
AHA	Not mutagenic or carcinogenic, not reproductive or developmental toxins, not skin sensitizers	Reduced Ca ion concentration in the epidermis disrupts cellular adhesions by removing Ca ions from the cell adhesions by chelation allowing for exfoliation, promoting cell growth, and retarding cell differentiation
Glycolic acid	Increased solar-stimulated radiation sensitivity in the human skin Increased epidermal and dermal levels of hyaluronic acid and collagen gene expression	Acceleration of collagen synthesis by fibroblasts and also modulation of matrix degradation and collagen synthesis through keratinocyte-released cytokines Accelerated epidermal turnover and inhibition of melanin formation in melanocytes by directly inhibiting tyrosinase activity
PHA	Photoprotective	Function as a chelating agent and exhibits potency in scavenging free radicals
SA	Enhances percutaneous penetration, not photosensitizer, not phototoxic	Acts at the level of transcription to downregulate the production of fibrinogen, fibronectin, and α-hemolysin virulence factors necessary for bacterial replication in host tissues

formulations, particularly with respect to skin irritation and barrier impairment.

The efficacy of both lactobionic and glycolic acid was higher when used in vehicles based on analkylpolyglucoside (APG) emulsifier, emphasizing the importance of vehicle on the effects of topical actives (Tasic-Kostov et al. 2010).

The safety profile and mechanism of action of the HAs are shown in Table . 3.

Clinical Uses of HAs

The indication for treatment with the HAs depends mainly on concentration, pH, formulation, and application time.

The higher the concentration and the lower the pH of the product, the greater the exfoliative, toxic, and corrosive action. Lower concentrations with 5–20% of HAs are formulated in creams or gels for use prior to peeling and for long-term application (Babilas et al. 2012).

Dry Skin and Hyperkeratinization

A large group of AHAs, when applied topically to patients with any form of hyperkeratosis, diminish the thickness of the stratum corneum by diminishing corneocyte cohesion, which is first seen at the lower, newly forming levels of the stratum corneum (Van Scott and Yu 1984).

Topical use of AHA formulations on xerotic skin restores the stratum corneum and epidermis to a more normal clinical and histologic state. Combination HA formulations that contain PHAs and BAs are found to have unparalleled efficacy for treating xerosis and for treating otherwise treatment-resistant conditions such as calluses and fissured plantar and palmar skin (Green et al. 2009).

For example, the use of a cream containing 5% lactic acid, 5% glycolic acid, 5% mandelic acid, and a 5% blend of gluconolactone and maltobionic acid (pH 3.7) once daily for 3 weeks improved hyperkeratotic heels. Moreover, lamellar ichthyosis may be treated successfully with the same combination, twice a day for 2 weeks (Green et al. 2009).

For usual severe cases of lamellar ichthyosis or X-linked ichthyosis, optimum effectiveness is achieved with unneutralized formulations as follows: glycolic acid, mandelic acid, saccharic acid, tartaric acid, malic acid at 5–10%, and gluconolactone at 10–20%. Lactic acid formulations partially neutralized with ammonium hydroxide have provided equivalent effectiveness

in 8–12% formulations. The preparations should be applied thinly 2–4 times daily for 1 to 3 weeks until the clinical appearance of the skin approaches normal (Van Scott and Yu 1984).

Sensitive Skin and Rosacea

One of the distinguishing benefits of the PHAs and BAs is their gentleness on the skin. Compared with glycolic acid and lactic acid, PHAs and BAs do not sting or burn. Previous studies have demonstrated compatibility with sensitive skin, even on rosacea and atopic dermatitis (Rizer et al. 2001a, b).

Moreover, partly because of their gentleness, concurrent use of products with gluconolactone and a topical drug containing azelaic acid has been shown to improve therapeutic outcomes for rosacea by reducing skin redness and diminishing the appearance of telangiectasia. The latter effect may occur as a result of the ability of gluconolactone to increase skin thickness. Patient tolerability of medication containing azelaic acid also improved (Draelos et al. 2006).

Hyperpigmentation

AHAs, such as glycolic acid and lactic acid, have been reported to be effective in treating pigmentary lesions including melasma, solar lentigines, and post-inflammatory hyperpigmentation. The proposed mechanism of this effect is epidermal remodeling and accelerated desquamation, which should result in quicker pigment dispersion (Kornhauser et al. 2010).

In 2003, Usuki et al. published an in vitro study that showed that glycolic acid and lactic acid (300–500 μg/mL) suppressed melanin formation by directly inhibiting tyrosinase activity in human and mouse melanoma cells. Both the transcription and translation of tyrosinase were decreased significantly, with reduced enzyme function. The authors concluded that glycolic acid and lactic acid might work not only by accelerating epidermal turnover but also by directly inhibiting melanin formation in melanocytes (Usuki et al. 2003).

Clinical studies showed that forearms treated with 25% lactic acid lotion, two times a day for 6 months, had fewer lentigines and less mottled hyperpigmentation and were more plumped (Green et al. 2009).

The use of PHAs also leads to significant skin lightening, although the mechanism by which that occurs has not yet been elucidated (Grimes et al. 2004).

Wrinkles and Photoaging

Ultraviolet (UV) exposure induces a wide range of damaging chemical reactions in the skin. Chronically exposed skin becomes photoaged, a condition characterized by a thicker dermis (degradation of the elastic fiber network with accumulation of breakdown products and deposition of lysozyme) and thinner epidermis with cellular atypia and loss of polarity, irregular pigmentation, wrinkling, and coarseness. Although the gold standard for treatment is tretinoin, the efficacy of hydroxy acids has been repeatedly reported (Piérard et al. 1999).

The antiaging benefits of AHAs have been known for many years. In ancient times, Cleopatra was said to bathe in sour milk, which contains lactic acid, in order to give her skin a youthful appearance (Tran et al. 2015).

The exact mechanism of action for topical AHAs is still unknown; however, the most widely accepted theory is that AHAs remove calcium ions from epidermal cell adhesions by chelation. This results in weakening of the intercellular adhesions, which has an exfoliating effect by causing shedding and flaking of dead and dry cells. The reduced calcium levels also promote further cell growth while slowing cell differentiation, thereby lessening the appearance of wrinkles and making the skin look younger (Tran et al. 2015).

AHAs may also promote increased gene expression of collagen and hyaluronic acid in the dermis and epidermis, which in turn improves plumpness and hydration of the skin (Bernstein et al. 2001).

Previous studies have found substantial increases in dermal thickness that were correlated

with increased amount of hyaluronic acid and other GAGs as well as with qualitative improvements in collagen fibers and improved histologic quality of elastic fibers. The papillary dermis also increased in thickness, with increase prominence of dermal papillae. The effects lasted for months (Ditre et al. 1996).

Glycolic acid also increases the production of collagen, hyaluronic acid, and fibroblast proliferation. Sun-damaged forearm skin was treated with 20% glycolic acid lotion or a lotion vehicle control (oil in water, pH 3.9), twice a day for 3 months. The authors found that this protocol increased epidermal thickness, epidermal and dermal levels of hyaluronic acid, and collagen gene expression. Even small increases in the content of cutaneous hyaluronic acid may result in large changes in epidermal and dermal hydration, affecting skin appearance, texture, and function (Bernstein et al. 2001).

Although GAGs make up only about 0.1–0.3% of the dry weight of the normal dermis, they can bind up to 1000 times their weight in water. Thus, relatively small alterations in the amount of dermal GAGs may result in large changes in epidermal and dermal hydration, affecting skin appearance, texture, and functional ability. GAGs provide an aqueous environment for cell migration, the diffusion of nutrients, and elimination of toxic metabolites. The early provisional matrix in a healing wound consists of fibrin and hyaluronic acid, creating a scaffold for the migrations of cells to the wound site. This allows for the creation of a more permanent, stable matrix composed largely of collagen. Thus GAG deposition is an early event in skin formation preceding the formation of collagen (Bernstein et al. 2001).

Epidermal GAG staining increased 2–2.5 fold after AHA treatment, with nearly identical results for retinoic acid. The dermal effects are also similar to tretinoin. Moreover, glycolic acid-treated skin showed a 2.8-fold increase in type I collagen mRNA, as compared to vehicle-treated control skin. Accumulation of collagen mRNA could be due to increased transcription or decreased mRNA stability, so future studies are needed to help determine the mechanisms of collagen mRNA accumulation (Bernstein et al. 2001).

Rendl et al. investigated the effects of creams containing lactic acid on the secretion of cytokines by keratinocytes in human reconstructed epidermis. They found that topically applied creams containing lactic acid (1.5%, 3%, or 5%) led to a concentration-dependent increase in apoptotic cells compared to the vehicle control. In addition, they found an increase in the secretion of vascular endothelial growth factor (VEGF) over the vehicle control after treatment with 1.5% or 3% lactic acid. The authors concluded that topical application of lactic acid modulates the secretion of cytokines by keratinocytes and that this regulation might represent a mechanism contributing to their therapeutic effects such as photoaging (Rendl et al. 2001).

Newman et al. investigated the histological and clinical effects of 50% glycolic acid peels on photoaged skin. It consisted of a split-face study of glycolic acid 50% versus vehicle once a week for 4 weeks. They assessed a decrease in rough texture and fine wrinkling, fewer solar keratoses, and a slight lightening of solar lentigines. The histologic analysis revealed a thinning of the stratum corneum, an enhancement of the granular layer, and an epidermal thickening, which shows that 50% glycolic acid peels are capable to improve mild signs of photoaging (Newman et al. 1996).

Ditre et al. conducted a placebo-controlled study with patients with moderate-to-severe photoaging. Patients had to apply an AHA-containing lotion (25% glycolic acid ($n = 5$), 25% lactic acid ($n = 5$), or 25% citric acid ($n = 7$), pH 3.5) twice daily for 6 months. There was a 25% increase in skin thickness; the epidermis showed a significant reversal of basal cell atypia, dispersal of melanin pigmentation, and a return to a normal rete pattern. The elastic fibers tented to be longer, thicker, and less fragmented. Ultrastructurally, the basal layer showed more uniform basal keratinocyte nuclei; less clumping of tonofilaments within the cytoplasm, with more perinuclear localization of tonofilaments; and the formation of microvilli. There were only transient tingling and itch sensation as side effects, but these became less noticeable or disappeared with continuous use. Increased skin thickness appears to be caused by increased synthesis of GAGs and collagen, and possibly elastic fibers (Ditre et al. 1996).

Bernstein et al. demonstrated the effects of citric acid in the epidermis and dermis of sun-damaged skin, but highlighted the main role of sunscreens (Bernstein et al. 1997).

Acne

For the treatment of acne-prone skin or mild acne, predominantly, cosmetic products containing HAs 5–20% are on the market. The pH value usually ranges from 2 to 8. However, the concentration and a pH significantly lower than the physiological pH of the skin are primarily responsible for the comedolytic and antimicrobial effects.

AHAs depending on the concentration used reduce the coherence of the superficial and also follicular corneocytes in the stratum corneum. In addition, because of pH changes, proteases like aspartase and cysteine proteases are likely to be activated in the outer stratum corneum, and, thus, the desquamation process could be enhanced as seen by an increased stratum corneum turnover time. Moreover, it is well known that decreasing the pH on the skin surface regulates and impairs microbial growth, in particular of *Propionium* bacteria.

A 10% glycolic acid containing oil-in-water emulsion improved mild acne applied as a monotherapy for 45 days, when compared to placebo. The application of glycolic acid formulation for 6 weeks led to a significant decrease in the pH from 6.2 to 5.4 in volunteers suffering from acne or acne-prone skin. An acidic pH on the skin surface exerts antibacterial effects, and it can be assumed that it yields a reduction of *P. acnes* in the treated patients. The tolerability of glycolic acid 10% is expected to be better when compared to benzoyl peroxide-containing products or topical retinoids. In addition, glycolic acid is not bleaching or discoloring textile, and antibiotic resistance is unlikely to occur (Abels et al. 2011).

Salicylic acid exhibits keratolytic properties as it solubilizes intracellular cement. Its lipid solubility permits the interaction with multilamellar structures surrounding the keratinocytes in the stratum corneum, thereby exhibiting follicular atrophy and comedolytic action within the sebaceous unit. SA is effective in comedonal and inflammatory acne. It also facilitates the resolution of post-inflammatory hyperpigmentation of the face (Kar et al. 2013).

Kessler et al. compared the efficacy of alpha- (30% glycolic acid) and beta-hydroxy (30% salicylic acid) acids as peel agents, in a split-face, double-blind, randomized controlled study on patients suffering from mild-to-moderate severe facial acne vulgaris. The acids were randomly applied to one side of the face every 2 weeks for a total of six treatments. Both peels reduced papules and pustules after the second treatment ($p < 0.05$) and did not differ in effectiveness. More adverse events were reported with the glycolic acid peel though (Kessler et al. 2008).

Uses as a Peeling Agent

Glycolic acid and lactic acid are AHAs that have been used commonly as peeling agents.

In high concentrations, up to 70% or greater, they can be applied to the skin for short times to achieve substantial desquamation and accelerate the epidermal and dermal renewal for rejuvenation and adjunctive care of acne, rosacea, and hyperpigmentation (Green et al. 2009).

HA peels are good options for pre- and post-treatment for laser resurfacing. A 50% glycolic acid peel 2 and 4 weeks before resurfacing and a 70% glycolic acid peel immediately before laser treatment (neutralize peel and begin resurfacing) may require fewer passes with the laser and result in fewer complications (Petratos 2000).

A study comparing the use of oral isotretinoin alone versus oral isotretinoin with 20% salicylic acid peels once every 2 weeks for 16 weeks concluded that both are effective but the clearance of acne was significantly better with combined therapy with no further adverse effects (Kar et al. 2013).

Synergy with Topical Drugs

HAs can be used to enhance and improve therapeutic effects of certain medicinal agents. For

example, the AHA lactic acid and its ammonium salt prevent dermal atrophy associated with the topical use of corticosteroids (Lavker et al. 1992). This is presumably due to AHA stimulation of collagen and GAGs synthesis.

It is possible that HAs may increase the affinity of the receptor molecule toward the topical agent, acting as a better and more efficient coenzyme or as an activator by disrupting barriers and removing inhibitors for better binding of the agent toward its receptor molecule. Such may be the case when AHAs are combined with topical corticosteroids in the treatment of psoriasis – the enhanced therapeutic effects are not due to increased penetration and can be achieved by the use of a combination formulation or by an alternative use of separate formulations (such as different morning/evening preparations). For example, there is better clinical response in the use of 0.5% benzilic acid added to clobetasol propionate 0.05% in the treatment of psoriasis than clobetasol propionate 0.05% alone (Green et al. 2009).

Conclusion

HAs is a class of substances which can be used as topical products or peeling agents. They represent good option for the treatment of hyperkeratinization, photoaging, hyperpigmention, and acne, with a high tolerance and good safety profile.

Take-Home Messages

- Hydroxy acids are safe and well tolerated even in a sensitive skin in proper formulations.
- The most important indications are acne, hyperpigmentation, and photoaging.
- Office-based treatments should be performed by trained dermatologists in order to avoid complications such as epidermolysis, blistering, scarring, persistent erythema, and post-inflammatory hyperpigmentation.

Cross-References

- ▶ Approach in Photodamaged Skin, Melasma, Acne, and Rosacea
- ▶ Chemical and Physical Sunscreens
- ▶ Evaluation and Classification of Aging
- ▶ Oral Photoprotection
- ▶ Photoprotection: Concept, Classification, and Mechanism of Action
- ▶ Skin Anatomy, Histology, and Physiology

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