

Discovering the 21st Century Fountain of Youth: A Discussion of the Effectiveness of Popular Anti-Aging Therapies

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Abstract

Physical appearance has a significant effect on social and psychological aspects of self-esteem and overall wellbeing. With physical appearance so highly emphasized by current society, many are seeking ways to look younger and healthier. As a result, anti-aging therapies are in demand and the market is constantly inundated with new products claiming to be the next best therapy for aging skin. Consumers as well as physicians often encounter difficulty in making informed decisions when choosing among treatment options.

Keywords: Anti-aging therapies; Skin aging

Introduction

A review of current literature can be a useful way to determine which therapies have undergone clinical testing and to assess and compare the outcomes of individual treatment modalities. During this process, critical assessment of the quality of studies is necessary in order to rule out studies with design flaws or excessive bias from corporate funders. Determining the level of evidence is also a useful tool in assessing the quality of a study. The Oxford Centre for Evidence-based Medicine [1] has developed a system of defining each level of evidence as follows: a systematic review with homogeneity of results reported from randomized, controlled trials (RCT) is classified as level 1a; an individual RCT with narrow confidence interval is classified as level 1b; all or none case series are classified as level 1c; a systematic review with homogeneity of cohort studies is classified as level 2a; an individual cohort study including low quality RCTs is classified as level 2b; "outcomes" research is classified as level 2c; a systematic review with homogeneity of case-control studies is classified as level 3a; individual case-control studies are classified as level 3b; case series are classified as level 4; and expert opinion without explicit critical appraisal or based on physiology or bench research is classified as level 5. Results reported within this review have all been derived from level 1 and 2 studies.

In order to evaluate the effects of various treatment modalities on aging skin, it is important to understand the fundamental changes, which occur to the skin and subcutaneous tissues over time. Skin aging is a result of the combined effects of accumulated reactive oxygen species (ROS), telomere shortening, decreased hormone and cytokine levels, and a decrease in melanocytes and Langerhan's cells. Reactive oxygen species cause damage to lipid membranes, cellular enzymes, and DNA leading to cumulative tissue damage. Aging skin is characterized by atrophy, dryness, and laxity [2]. Intrinsic factors, such as programmed genetic changes, as well as extrinsic factors, such as sun exposure, and toxins including those from smoking, play a significant role in skin aging [3].

The primary focus of youth preservation is the face, as this is often our first impression of a person's age. Evidence of an aging face manifests as thinning skin, pigmentation changes, static wrinkle presentation with deepening facial folds, and sagging of the subcutaneous fat compartments. Epidermal thinning and loss of collagen leads to loss of skin elasticity [4]. Wrinkling results from a loss of facial fat combined with gravity and muscle pull. The aging face also undergoes many anatomical changes including descent of the brow and lower eyelid, changes in the contour of the upper eyelid, deflation of the infraorbital skin envelope, increased visibility of the lid-cheek junction and nasojugal crease, increased prominence and depth of the nasolabial fold, and development of marionette lines and jowls [5,6]. Bony remodeling also plays a role in the - aging face, with areas of the face undergoing specific and predictable resorption with aging. Specific areas of resorption include the superior and inferior alveolar bones, as well as supero-medial and infero-lateral orbit [7]. Twin studies have shown that smoking is associated with significant worsening of upper eyelid skin redundancy, lower lid bags, malar bags, nasolabial creases, jowls, upper lip lines, and lower lip vermilion lines than would be expected for one's chronological age, sun exposure, and genetics [8]. These superficial and anatomical changes are the targets of current facial rejuvenation therapies.

Clinical evaluation is the most frequently used tool to quantify the degree of age related changes before and after treatment, either in-person or via digital photography. Clinical scoring using validated assessment scales has proven to be highly reliable for the evaluation of the signs of facial aging including forehead lines, nasolabial folds, marionette lines, jawline, oral commissures, neck volume, glabellar lines, infraorbital hollow, upper cheek fullness, crow's feet, lip fullness, and lip wrinkles [9-12]. Though assessment scales have been used frequently to assess firmness, hyper pigmentation, fine lines, blotchy redness, tactile roughness, and clarity, they have yet to be validated. Alexiades Armenkdis developed and tested a scale along with formulas that have been widely used to quantify and calculate the percent improvement after treatment of individual parameters of skin aging, such as rhytides, laxity, dyschromia, elastosis, erythema-telangiectasia, texture, keratoses, and patient satisfaction [13].

In addition to clinical assessment scales, other assessment tools exist but are less frequently used. Skin surface topography using silicone impression-based grading is both a valid and reproducible measure of photo aging and dermal elastosis [14,15]. Biopsies may be used to histologically assess increases in collagen and elastin deposition or epidermal thickness but are invasive and leave scars. Newer measurement technologies include the corneometer which measures hydration of the epidermis, cutometer which measures skin elasticity, and digital programs such as VISIA which combine multispectral imaging and complexion analysis software to quantify certain characteristics of the skin topography and subsurface such as UV damage, brown spots, fine lines, texture, pore size, and redness. This review will focus on the evidence behind various novel and traditional anti aging therapies that have been popularized in recent years with emphasis on those that are strongly proven to be effective.

Sunscreen

Exposure to UV radiation is a well-established factor in the acceleration of aging. Sunscreens block UV penetration of the skin and are an essential component of any anti-aging regimen. Though the benefit of sunscreen use for the prevention of skin aging has been demonstrated in animal models [16,17], evidence of such benefits in humans has been lacking in the literature.

Recently, a randomized, controlled trial by Hughes et al. [18] tracked changes in skin aging in 903 adults aged 25-55 over for 4.5 years. Participants were randomly assigned to one of four different groups including: daily use of broad-spectrum sunscreen and 30 mg of carotene, daily use of sunscreen and placebo, discretionary use of sunscreen and 30 mg of carotene, and discretionary use of sunscreen and placebo. There were no differences in skin phenotype, sun exposure, pre-trial sunscreen use, or treatment compliance between groups. Upon completion of the trial, 77% of daily sunscreen users reported application of sunscreen at least 3-4 times per week versus 33% of discretionary users. Skin changes were assessed for differences pre-treatment and post-treatment using silicone-based replicas of the back of the hand in accordance with the Beagley and Gibson scale of microtopography. Results of the assessment showed no detectable increase in microtopography grade in the daily sunscreen group. These participants showed no progression of photo aging after 4 years of treatment. Skin aging advanced by 24% in the discretionary sunscreen group compared to the daily sunscreen use group (relative odds, 0.76 [95% CI, 0.59 to 0.98]). There was no difference in microtopographic changes between groups assigned to carotene supplementation versus placebo. Because an increase by only one unit on the microtopography scale is associated with worsening of skin coarseness and wrinkling along with an increased risk of actinic keratoses and skin cancer [19,20], the use of sunscreen was associated not only with cosmetic benefit but also with a reduction in the progression of malignant changes. Reported adverse effects of sunscreen are rare and mild including: contact allergy or skin irritation (3%), greasiness (1%), and interference with perspiration or stinging eyes after facial perspiration (0.8%) [21]. Thus, daily sunscreen use is not only painless and inexpensive, but also the most effective intervention to lessen the continuation of photo aging and cutaneous malignancy caused by UV exposure.

Antioxidants

In recent years, antioxidants have been regarded as a panacea, but are the effects on skin supported by evidence? Free radicals cause

damage to DNA, lipid membranes, and protein structures within cells, leading to photocarcinogenesis and photo-aging [22]. Free radicals or reactive oxygen species (ROS) also alter the structure of the skin by diminishing transforming growth factor-beta, which results in decreased collagen synthesis and increased elastin production [23-25]. Antioxidants have the ability to neutralize free radicals created in the skin due to UVA radiation exposure, toxins, and metabolic processes; and consequently protect the skin from aging and cancer. The body produces its own natural antioxidants, including superoxide dismutase, catalase, and glutathione (GSH) peroxidase. However, body stores are rapidly depleted when faced with excess UVA exposure and pollutants [22]. In addition, concentrations of antioxidants in the skin decrease with aging. Elderly subjects have 70% less alpha-tocopherol, L-ascorbic acid, and total GSH than their younger counterparts [26].

Topical antioxidants have been developed in an effort to maintain antioxidant concentrations in the skin. There are many sources of antioxidants, among the most common are vitamins C, E, A, selenium and tea polyphenols. These compounds can be combined for synergistic effects. For example, 15% L-ascorbic acid and 1% alpha tocopherol double the protection against UV induced erythema, sunburn, and thymine dimer formation versus ascorbic acid alone [27]. Due to their protective action within the skin, antioxidants are being increasingly incorporated into sunscreens and other skin care products. Unfortunately, antioxidants are unstable. In the case of vitamin C, esterification is required to stabilize the compound and increase topical penetration. However, esterification also diminishes the antioxidant power of the product [28-30]. Therefore, improved topical delivery is often achieved at the expense of antioxidant capacity. Even though sunscreens with added antioxidants have proven to protect against the effects of photo-exposure to a greater extent than sunscreen alone [31,32], this is not true of all products on the market.

Wang et al. [33] tested 13 popular commercial sunscreen products containing antioxidants according to 3 in vitro UVA labeling indices, including the new FDA proposed guidelines, and found that nearly all had either limited or no antioxidant effect. Despite product claims to include antioxidant protection, support is often lacking. In response to this issue, a trial by Palmer et al. [34] demonstrated the importance of quantifying antioxidant activity in order to produce an effective anti-aging product. In order to ensure high levels of antioxidant activity in their product, ORAC testing was utilized. Total Oxygen Radical Absorbance Capacity (ORAC) is used by the U.S. Department of Agriculture to quantify antioxidant capacity of both foods (ORAC_{fn}) and skincare products (ORAC_{sc}). While the average antioxidant skincare product averages an ORAC_{sc} score of 6,970 micromole TE/g, the regimen used in the trial scored within a range of 18,000-79,000 micromole TE/g for each of the various products. The regimen consisted of a facial wash, daily lotion, eye serum, and night crème, each including antioxidants in the form of coffee fruit extract and concentrated fruit and vegetable extracts. The control group regimen consisted of a control facial wash and a control moisturizer for day and night. Participants were selected based on mild-moderate facial photo damage and dryness and had to have used a moisturizer at least twice daily and a daily UVA/UVB facial sunscreen of SPF 30 or greater. Before the trial, participants underwent a 2-5 day washout period for all moisturizers, a 30 day washout period from all anti-aging products, a 6 month washout period for all prescription anti aging products, and a one year washout period for any cosmetic procedures. This 12-week, double-blind, randomized, controlled clinical trial enrolled 40 Caucasian females between the ages of 45-60 years,

Fitzpatrick skin type I-IV, and Glogau score of II or III. Facial skin was evaluated before and after treatment based on clinical assessment using a 9-point scale including assessment of wrinkles, firmness, hyper pigmentation, blotchy redness, tactile roughness, and clarity. Clinical assessment was supported by digital photography, multispectral imaging and complexion analysis software (VISIA), silicone replicas of the crow's feet area, corneometer, cutometer, and participant self-assessment. Analysis revealed a significantly greater improvement in all parameters in the test group over the control group, including improvements in wrinkles (69.5% vs 9%), firmness (100% vs 81.8%), hyper pigmentation (78.2% vs 35.3%), blotchy redness (82.6% vs 45.4%), tactile roughness (100% vs 81.8%), and clarity (100% vs 81.8%). No adverse effects have been reported in the literature with the use of topical antioxidants. High antioxidant capacity products are an effective way to moderately reverse the various signs of photo aging. For best results, products that have been tested to ensure antioxidant activity are recommended.

Retinoids

Retinoids, vitamin A derivatives, have drastically improved the field of anti-aging skincare over the last several decades. Tretinoin, or all-trans-retinoic acid (RA), was the first topical prescription medication to demonstrate reversal and repair of both photo aging and intrinsic aging [35-38], and has been approved for this use since the 1990's [39]. RA has been extensively studied and consistently demonstrates significant improvements in fine facial wrinkles [40-42], mottled hyper pigmentation, and skin roughness [43-48] after 12 weeks of use, with further improvement after continued use [49-51]. RA interacts with nuclear receptors within the cell to influence epidermal proliferation and differentiation [52,53]. Through this mechanism, RA is able to counteract the thinning of the skin associated with aging by stimulating the synthesis and deposition of collagen and fibrillin. RA also diminishes the collagen degrading activity of matrix metalloproteinase's [53,54].

Retinol is the lipophilic precursor to RA and easily penetrates skin, where it is metabolized by keratinocytes. Retinol is very unstable in the presence of air and light, but recently, formulations have been developed to increase stability and to extend shelf life. Techniques include esterification with palmitate or acetate to create retinyl palmitate and retinyl acetate. Increased stability has greatly contributed to the formulation of OTC products, expanding the accessibility of this treatment. However, studies suggest that while retinol may be less irritating to the skin than RA, it is also less potent [55-57].

Until a 2012 study by Ho et al. [58], it was generally accepted that OTC retinol is not as effective as prescription retinoic acid. Ho et al. [58] conducted a randomized, double blind, controlled trial, comparing the effectiveness of non-prescription tri-retinol 1.1% vs. prescription Tretinoin 0.025% in 38 female participants aged 35-65 with Fitzpatrick skin type I-IV and mild to moderate facial photo damage. The tri-retinol formula included retinol, retinyl palmitate, and retinyl acetate. Stability testing demonstrated maintenance of 95% of the initial concentration after 3 months. Clinical assessment on a nine-point scale with half-point increments was used to evaluate participants for fine wrinkles, coarse wrinkles, skin firmness, skin tone/brightness, mottled pigmentation, tactile roughness, and global photo damage improvement. In all parameters, there was no significant difference between the two treatments. Thus, the authors concluded that it is possible to formulate an OTC retinoid product

that is as effective as prescription RA. It is important to note that the lowest available strength of RA (0.025%) was selected for comparison to the tri-retinol formulation. Efficacies of higher concentration RA might yield different results. Adverse effects of retinoid use include overall mild erythema, dryness, scaling, peeling, burning, stinging, itching, and tightness. The use of moisturizer can help diminish these effects. Retinoids also increase photosensitivity, requiring the use of daily sunscreen. All adverse effects were rated as mild in both the tri-retinol and RA groups. The tri-retinol group maintained erythema throughout the course of treatment, while the RA group peaked and diminished after 4 weeks. Retinoids appear to be a universally effective treatment choice for all skin types and levels of photo damage. Because RA is also an effective treatment for acne, it is a sensible treatment choice in patients who suffer from acne and also demonstrate signs of photo damage. Over-the-counter retinoid products should be selected carefully due to variations in stability and effectiveness among different formulations.

Chemical Peels

Another common minimally invasive procedure to fight the signs of aging is chemical peels. Chemical peels consist of controlled destruction of the epidermis with or without the dermis in order to remove superficial lesions and allow for regeneration of tissue to correct defects. Chemical peels are ideal for patients with wrinkling, loss of elasticity, as well as irregular pigmentation and actinic keratosis from photo damage. These patients must be distinguished from patients with gravitational effects of aging and volume loss who require surgical correction. However, chemical peels are a good supplement to the surgical options to give a more youthful surface appearance. The ideal chemical peel patient has fair skin with mild, shallow wrinkles. Relative contraindications to chemical peels include cutaneous radiation history, smoking, active or frequent HSV infections, diabetes, and tendency for hypertrophic or keloid scars. Elevated levels of estrogen, such as in pregnancy or with the use of OCPs, and photosensitizing drugs cause hyper pigmentation and should also be avoided. Patients are recommended to avoid pregnancy during or within the first 6 months of a peel. Concurrent or recent isotretinoin use is an absolute contraindication [59,60].

Chemical peels are categorized according to peel depth: superficial, medium, and deep. Superficial peels, using alpha hydroxy acids and beta hydroxyl acids or Jessner's solution (14 g salicylic acid, 14 g lactic acid, 14 g resorcinol in 100 cc ethanol), result in epidermal sloughing and an inflammatory response in the upper papillary dermis while stimulating collagen production. This is reserved for patients with mild photo damage, superficial lentigines, and fine wrinkles. Medium peels, using Jessner's peel or CO₂ and 35% trichloroacetic acid (TCA) solution, slough the epidermis and cause variable amount of necrosis and inflammation in the papillary dermis. Medium peels are reserved for patients with epidermal growth, moderate photo damage, and mild to moderate wrinkles or acne scars. These peels avoid inflammation in the reticular dermis, minimizing the adverse effects of deep peels. Deep peels, with increased concentration of TCA solution or phenol, slough the epidermis and papillary dermis and cause inflammation of the reticular dermis. These are reserved for deep wrinkles but increase the risk of scarring and hypo pigmentation [61,62].

Various chemicals have been used as superficial peeling agents, most commonly being alpha-hydroxy acids, such as glycolic acid, or beta-hydroxy acids, such as salicylic acid. A recent study compared the efficacy of two types of superficial chemical peels, glycolic acid (GA)

and capryloyl salicylic acid (LHA), a novel derivative of salicylic acid. Volunteers were randomly assigned to treatment of one side of the face with LHA vs. GA in increasing concentrations as tolerated and then compared. At 12 week follow up, 41% of LHA-treated and 30% of GA-treated subjects demonstrated significant reduction of fine lines/wrinkles. Also notable, 46% of LHA subjects and 34% of the GA subject's demonstrated reduction in hyper pigmentation compared to baseline. The study concluded the 5-10% LHA peel to be as effective as 20-50% GA peel in reducing fine lines/wrinkles and hyper pigmentation suggesting LHA to be a viable alternative [61].

Langsdon et al. [62] recommend pre-peel preparation with exfoliation, hydration, and sun protection. Patients are recommended to use sunscreen with SPF 30 or higher and a facial exfoliant cream containing glycolic acid for at least 2 weeks before the procedure. Tretinoin can be used in patients with thick, oily skin and hydroquinone can be used in patients with significant hyper pigmentation or melasma. Authors also recommend increasing TCA doses between sessions from 15% to 35% for best wrinkle and photo damage reduction [62].

Another study recommends the use of glycolic acid combined with 35% TCA in medium depth peeling. Thirteen patients underwent treatment with 70% GA plus 35% TCA to one side of the face and Jessner's solution plus 35% TCA to the other side of the face. The GA-TCA peel was more effective at reducing actinic keratosis than the JS-TCA peel. The JS-TCA peel resulted in a stronger inflammatory response with more neovascularization and fibrosis while the GA-TCA peel resulted in more neoelectogenesis. The GA-TCA peel may also be more effective in correcting damaged elastic fibers. Authors concluded that the GA-TCA combination is an effective option for medium depth chemical peeling in treating photo damaged skin [63].

Concern has been raised regarding the carcinogenicity of trichloroethylene (TCE) and its oxidative metabolite, trichloroacetic acid (TCA). One study examined chronic inhalation assays and oral gavage in mice and implicated TCA as a cancer-causing compound, independent of TCE exposure [64]. Another study demonstrated cytotoxic and genotoxic effects of TCA on human lymphocytes *in vitro* [65]. The National Toxicology Program (NTP) has classified TCA as "reasonably anticipated to be a human carcinogen" based on these and similar studies [66]. As TCE is used as an industrial solvent, people in professions involving years of exposure to this chemical have been shown to develop liver cancer, kidney cancer, and non-Hodgkin's lymphoma; however, these reports are based on small pools of subjects and are confounded by the presence of other solvents and carcinogenic risk factors in the workplace [67]. We are unsure of the actual potential of cancer caused by TCA peeling as there are no human *in vivo* studies assessing this risk. Chemical peel procedures involve exposure to TCA for only a short period of time and no evidence of carcinogenesis following this limited exposure has ever been documented.

Neuromodulators (Botox™, Dysport™, Xeomin™)

Botox (botulinum neurotoxin) treatment has been a mainstay in non-surgical facial rejuvenation for over 20 years. There are several forms of botulinum neurotoxin, but only botulinum neurotoxin type A (Botox™, Dysport™, Xeomin™) is approved in the US for cosmetic purposes [68]. While Botox is officially indicated for the temporary improvement of moderate to severe glabellar lines in adults

65 and younger, it is widely used off-label for other anti-aging purposes including correction of horizontal forehead lines and crow's feet [69].

One of the major advantages of neuromodulators is the ability to individualize each patient's treatment plan by altering both the dosage and the treatment areas according to each patient's needs. Furthermore, treatment plans are often combined with other anti-aging therapies including retinoids, lasers, and fillers as needed. Botox has been shown to be safe, not only in the short term, but even after repeated treatments [68]. In a meta-analysis of 36 studies involving 2309 subjects, no serious adverse effects were reported and the level and duration of efficacy was maintained over repeated rounds of injections with no major safety concerns [69].

The most frequent adverse effects following Botox treatment (reported by >5% of patients in clinical trials) are headache, respiratory tract infection, blepharoptosis, back pain, acne [69] and bruising [68]. These effects are minor and can generally be managed with simple interventions [68]. In addition, the rates of ptosis generally decrease with increased clinician experience [69]. In 2009, a black box warning was issued for BoNT-A products related to diffusion of the toxin beyond the treatment site. However, this effect is rare and is usually related to non-aesthetic uses of Botox [68]. Another rare complication of Botox treatment is the formation of neutralizing antibodies against a particular form of botulinum neurotoxin. In this case, the Botox treatments decrease in their efficacy after repeated use. Switching to a different formulation of botulinum neurotoxin (such as BoNT-B) restores the efficacy of the treatments. The effect of neutralizing antibodies could become more problematic in the future with the aesthetic market shifting towards a younger population of recipients who receive the treatments for a greater number of years [68].

Fat Grafting and Stem Cell Transplants

Volume loss has been recognized as a vital, if not primary, cause of facial aging [70]. The realization of the contribution of volume loss to facial aging initiated the "conservation of tissue" paradigm of facial rejuvenation 15 years ago. Maintaining the fat and skin volume of the face is not only important for maintaining a youthful looking appearance, but also for avoiding the "operated on" look in patients who have undergone facial surgery [71]. The increased demand for minimally invasive procedures with minimal downtime, as well as the ease of obtaining autologous adipose tissue has contributed to the emergence of fat transplantation as a mode of anti-aging therapy [72].

Autologous fat grafting, sometimes referred to as fat transfer, lipoinjection, or liposculpture, is performed by aspirating fat tissue from one area of the body and injecting it into another. There are many cosmetic applications, including lipoatrophy or asymmetry of the face, lip and facial augmentation, anti-wrinkle therapy [73]. And reconstructive use in patients with scars, radiation damage, and chronic ulcerations [74]. For anti-aging purposes, it is often injected into the periorbital region, cheeks, nasolabial folds, and perioral region [71]. Experimental evidence has shown that fat grafting increases volume in the face by a combination of neovascularization and survival of transplanted pre-adipocytes and adipocytes as well as fibrofatty tissue replacement due to inflammation created in the transplantation process [72].

Autologous fat has many properties of the "ideal filler." It is safe (non-immunogenic, non-carcinogenic, non-teratogenic), effective

(looks and feels natural, reproducible long term benefit), and practical (cost effective and easy to use) [74]. It is also durable and one harvest can give an abundance of transferrable fat that can be frozen and stored for 1 year [71]. This storing of adipose allows for “touch up” procedures if necessary, albeit at a lower long-term survival than “fresh” fat. Also, in addition to augmenting facial volume, fat grafting has also been reported to improve the quality and texture of the aging skin [74], which has been attributed to the significant stem cell population in the transferred fat [70].

The two major potential problems in fat grafting are variable resorption of adipose over time, and the potential for contour deformities [70]. Other complications include edema and bruising, which rarely last greater than 2 months. More severe, yet rare complications include graft necrosis, infection, and damage to underlying structures, blindness, and stroke. It often takes 3-6 transfers for optimal augmentation. It is important to avoid overcorrection in one session, because fat survival is better when overall amounts are small (1-3 cc) in each area and minute deposits (0.1cc) are implanted [72].

A prospective longitudinal study by Guijarro-Martinez et al. [74] used photographs to measure the efficacy of fat grafting. Photographic documentation was obtained for 9 patients pre-procedure and at 3, 6, 12, and 24 months post-procedure. Patient satisfaction was evaluated using a visual analogue scale (VAS) ranging from 1-10 at 18 months post-op. High patient satisfaction was reported (8.7 average VAS). Retrospective analysis of the photo documentation showed progressive volumetric decrease for up to 6 months post procedure. Volume seemed to stabilize at about 3-4 months, but a subtle decrease sometimes occurred for up to 1 year. Beyond that, volume was demonstrated to remain constant for 8-12 years [74]. Another prospective study by Fontdevila et al. [75] evaluated the long term viability of malar fat grafting using CT scans to volumetrically measure fat tissue. This study found that there was a statistically significant improvement in facial fat volume up to 12 months post procedure, and that it actually increased from the 2 months to the 12 months post procedure follow up. The contrasting results from these studies and the absence of clear, consistent, objective evidence of the survival of fat grafts is the reason why many plastic surgeons choose to use other fillers for facial volume replacement. However, the most experienced plastic surgeons have reported clinical results showing both short and long term persistence of transferred grafts and promote autologous fat as the ideal soft tissue filler [75].

Adipose derived stem cells (ADSC) can be isolated from the lipoaspirate used for fat grafting and are now being injected as an addition to the autologous fat graft [76]. While the injection of additional ADCs in fat grafts still requires IRB approval, this technique has already shown many benefits, including enhanced angiogenesis, improved graft survival, and reduction in graft atrophy [73]. The mechanism of the stem cells’ graft enhancement has not been completely elucidated, but they are thought to work by contributing to neo-angiogenesis in graft tissues. Stem cells act as endothelial progenitor cells or angiogenic factor releasing cells and are known to secrete angiogenic factors such as VEGF and hepatocyte growth factor. In vitro, they demonstrate the ability to proliferate in response to a hypoxic insult remote from their resident niche. Additionally, further in vitro studies show increasing ADSC proliferation with greater degrees of hypoxia [76].

There are several advantages to using adipose derived stem cells in fat grafts. They are an easily attainable source of adult stem cells

(1:100-1:1500 cells) compared to other tissues such as bone marrow, where the percentage of stem cells is not as high. The additional cost per procedure of using stem cells in the fat graft is negated by the fact that fewer touchup procedures have to be performed on those patients postoperatively than they do for the fat grafts without stem cells [76]. A prospective trial by Sterodimas et al. [76] compared fat grafting with and without the addition of adipose derived stem cells.

Twenty patients with congenital or acquired facial defects were randomly divided into 2 groups: 10 treated with autologous fat transplantation: 12-165 mL per session (group A), and 10 were treated with ADSC enriched lipografts: 8-155 mL per session (group B). Patients were followed at 6, 12, and 18 months post treatment and were asked to rate their overall satisfaction with their post treatment facial appearance on a validated [72] 5 point scale (1=poor, 2=fair, 3=good, 4=very good, 5=excellent). In group A, 3 patients achieved aesthetically acceptable results after a single treatment, but the remaining 7 required additional sessions of autologous fat grafting (3 had one additional treatment, 4 needed 2 additional treatments). All of the patients in group B required a single treatment session. Analysis of patient satisfaction clearly demonstrated better results in group B, maintained until 18 months. However by 18 months, there was no statistical difference between the groups in terms of patient satisfaction [76]. This study demonstrates that the addition of ADCs to fat grafts allows for fewer treatment sessions and improved cosmesis between sessions.

Ablative Fractionated Photothermolysis (AFP)

Laser resurfacing began with ablative CO₂ lasers, which rapidly advanced to become the standard for non-operative wrinkle reduction. However, ablative lasers not only required 2-3 weeks for re-epithelialization, resulting in 3-4 months of postoperative erythema, but also carried significant risks of scar and dyspigmentation. In response to these cosmetic issues, non-ablative lasers were developed in an attempt to similarly augment collagen formation and tighten tissue without disrupting the layers of the skin. Unfortunately, with improved safety came reduced efficacy. It was not until 2008 with the release of an ablative fractionated laser (AFP) that the most effective results could be produced with less risk.

Unlike the original ablative lasers, which fully remove the top surface of the skin, fractionated lasers create closely spaced, but spatially distinct micro-ablations that are able to safely treat greater depths within the dermis. Additionally, the presence of surrounding areas of unaffected dermal and epidermal tissue between ablations allows for enhanced wound healing and tissue contraction, resulting in a more rapid recovery, greater efficacy of treatment, and reduced occurrence of adverse effects such as scarring and dyspigmentation.

AFP is effective for the reversal of photo damage, pigmentation, collagen breakdown, and laxity. AFP also produces greater improvements in skin tightening and texture compared to NAFLP. Many types of fractionated laser treatment modalities currently exist, including erbium-doped yttrium aluminum garnet (Er:YAG) and yttrium scandium gallium garnet (YSGG). A study by LaTowsky and colleagues showed statistically similar effectiveness amongst four fractional laser devices up to 6 months post treatment, including Active and Deep (CO₂), Fraxel Repair (CO₂), Quadralase (CO₂), and Pearl (YSGG) [77,78]. Fraxel Repair pain scores ranged higher than other devices and resulted in the most pinpoint bleeding, but was the most time efficient device and produced the highest patient

satisfaction at 1 month post treatment; Active and Deep also caused pinpoint bleeding, but patients scored it highest for ease of healing and willingness to repeat treatment [79].

In order to quantify the effects of ablative fractionated phototherapy, Tierney et al. [78] followed 45 patients (39 women) aged 45-75 of Fitzpatrick skin types I-III throughout 2-3 sessions (mean 2.4) of treatments. Patients experienced pinpoint bleeding up to 48 hours post-treatment; edema, crusting, and severe erythema up to 72 hours post treatment; and moderate erythema for up to one week post treatment. However, there were no cases of scarring, post-inflammatory dyspigmentation or infection. Blinded physician photographic assessments occurred at 6 months post-treatment, based on a modified scale by Alexiades-Armenakas [79]. Treatment resulted in 48.5% mean improvement in skin texture, 50.3% mean improvement in skin laxity, 53.9% mean improvement in dyspigmentation, and 95% mean improvement in overall cosmetic outcome. The authors credited AFP with significantly greater improvements than those seen with NAFP devices. NAFP has lasting effects with 74% of improvements maintained at 2 years post treatment [80]. Additionally, ablative fractional phototherapy has been proven to be safe and effective for tightening of skin in the neck [81] and for the treatment of photo aged peri-ocular skin, including areas within the orbital rim [82].

Photodynamic Therapy

For patients who are not ready for aggressive treatments such as ablative skin rejuvenation, photodynamic therapy (PDT) is a milder option with results that are still more effective than non-ablative rejuvenation methods. PDT was originally approved to treat actinic keratosis, but off-label uses include treatment of malignant lesions of the skin such as superficial basal cell carcinoma and Bowen's disease. Following treatment, clinicians also noted reversal of the signs of photo aging including improvement of dyspigmentation, skin texture, fine lines, and overall complexion [83]. Since this discovery, PDT has been further developed for the purpose of photo rejuvenation.

PDT begins with topical application of a photosensitizer. The photosensitizer is absorbed and concentrated within premalignant and malignant cells to a greater extent than, non-damaged cells. A light source is used to activate the photosensitizer, creating reactive oxygen species (ROS) that selectively destroy the cells with higher photosensitizer concentration [84]. While common light sources include intense pulsed light (IPL), light emitting diode (LED), and lasers, non-laser light sources can be used to cover large surface areas, such as the face, in less time. The ROS created by this method have a short life span and therefore have a low mutagenic potential for extensive or systemic DNA damage [85]. Two photosensitizers, 5-aminolevulinic acid (ALA) and methyl aminolevulinate (MAL), are approved for dermatological use. Of note, the IPL-ALA combination has proven to be safe and effective for use on darker skin-types (Fitzpatrick III-IV) [86]. Compared to IPL alone, Dover et al. [87] found ALA-IPL treatment to have significantly greater improvements in global score for photo aging (80% vs 45%; $P=0.008$), fine lines (60% vs 25%; $P=0.008$), and mottled pigmentation (85% vs 20%; $P<0.001$); however, this combination was also associated with more adverse effects such as erythema (50% vs 15%), scaling and dryness (50% vs 15%; $P=0.04$), edema (50% vs 10%; $P=0.04$), and crusting with vesiculation (20% vs 5%; $P=0.11$). A histologic and morphometric study by Issa et al. [88] demonstrated a significant increase in collagen

and decrease in solar elastosis at 3 months with continued improvements 6 months post-treatment with red light and MAL.

There is no standardized protocol for PDT for photo rejuvenation as far as optimal incubation time, photosensitizer concentration, light dose, and number of sessions. The varied results reflect user dependent technique for application and the paucity of literature on the subject. In a review of the existing literature by Karrer et al. [89], PDT was upheld as an effective method for the reversal of fine lines and reduction of tactile skin roughness along with improvement of skin smoothness, actinic elastosis, skin color, and hyper pigmentation. PDT has less effect on coarse wrinkles and sebaceous gland hyperplasia; however, PDT with IPL is especially effective for the removal of telangiectasias and improvement of mottled hyper pigmentation. Another benefit of PDT is that adverse effects are generally mild to moderate, with erythema reported most often and occasional reports of crusting or mild superficial peeling. Although results are seen after one session, most studies are designed to include 3 sessions for maximal results. PDT is an advantageous form of photo rejuvenation due to its ability to affect multiple parameters of skin aging while also targeting AK and other dysplastic cells.

Combination AFT and PDT

As successful anti-aging therapies are discovered, combinations of therapies undergo evaluation for synergistic effects. Recently, a study by Haedersdal et al. [90] tested the effect of fractional CO₂ laser pretreatment on uptake of the photosensitizing agent MAL for PDT. AFT was used in Yorkshire swines to create tunnels through which MAL could penetrate deeper into the dermis and elicit a full thickness response from subsequent PDT. Results confirmed the hypothesis of deeper penetration with significantly greater levels of PDT activity, i.e. PpIX fluorescence and PpIX photo bleaching, extending into the deep dermis and subcutaneous fat compared to superficial extension with MAL-PDT alone. They concluded that penetration of photosensitizer is the main limiting factor in PDT, not penetration of the light source. Adverse effects included slight to intense erythema and pronounced inflammatory response. This combination is in the early phases of testing, but offers a promising possibility for boosting the effectiveness of PDT in future clinical practice.

Surgery

Many patients elect to undergo aesthetic facial surgery in an effort to reverse signs of aging. Options include rhytidectomy, upper face reconstruction with or without blepharoplasty/brow lift/forehead lift/orbital suspension, perioral reconstruction, and neck reconstruction. Most surgical reconstruction is combined with fat grafting, fractionated lasers, fillers, and or botulinum toxin treatment. It is important for patients undergoing any procedure to understand that the skin progressively tightens over time, requiring 6-12 months to see full results. Aesthetic facial surgery is typically a rewarding experience with good results. A recent study assessed perceived ages of patients before and 6 months after surgery. Patient ages were estimated to be 1.7 years younger than their chronological age before surgery and 8.9 years younger than their chronological age after surgery, with more dramatic results in face and neck lift, upper and lower blepharoplasty, and forehead lift surgeries over face and neck lift surgeries alone [91].

Face

Older patients commonly request “facelifts” to address complaints of facial volume loss and ptosis. Options for facelift include superficial vs. deep-plane traditional rhytidectomy, limited incision approach, and suspension suture lifts. The degree and location of ptosis, extent of volume loss, and extent of malar fat pad descent are important factors to consider. Ideal patients for minimally invasive procedures have minimal skin laxity, good elasticity, no platysmal bands, and no deep cervical creases [92].

The traditional rhytidectomy is divided into superficial and deep plane techniques. Both methods target the superficial muscular aponeurotic system (SMAS), a fibromuscular layer that is deep to the dermis but superficial to the musculoaponeurotic system. It encompasses and distributes force among the facial muscles. Superficial rhytidectomy technique involves either lifting a subcutaneous skin flap or a skin-SMAS flap and redraping the skin temporally and postauricularly, with fixation of the SMAS to the mastoid bone [93]. Deep-plane rhytidectomy is more involved but addresses the problem of malar fat pad descent that occurs with aging and allows for optimal management of the nasolabial fold. A composite flap including the orbicularis oculi muscle and malar fat pad is elevated at the sub-SMAS level and anchored posteriorly [94]. A retrospective study comparing SMAS plication versus deep plane supports SMAS plication in patients under 70 years old and deep-plane in patients older than 70 years old. Older patients benefited more so from the deep-plane procedure, compared to the insignificant difference in younger patients [95]. A common complication of these operations is facial nerve paresis.

Limited-incision techniques remove the need for postauricular incision and allow for less noticeable scarring. The limited-incision facelift (LIF) with lateral SMA Sectomy, S-lift, and minimal access cranial suspension lift (MACS-lift) all involve a preauricular incision with superficial dissection and varied levels of SMAS dissection and reapproximation [96,97]. These operations differ in incision location and anchoring sites. The S-lift and MACS-lift implement sutures to raise the SMAS and jowls like the LIF with lateral SMASectomy, but do not include platysma resection. S-lift is ideal for younger patients with less ptosis, while MACS-lift is ideal for ptosis of the nasolabial folds and malar fat. The MACS-lift can be simple or extended [98]. The suspension suture lift can be performed with or without the standard rhytidectomy and can be performed closed or open. Ideal patients have poorly defined mandibular border and no significant jowls [99,100]. Suture suspension is better for younger patients with only mild to moderate ptosis while barbed sutures are used more for older patients with volume loss [101]. Barbed sutures generally supply less lift but add more volume to the midface [102]. Common complications include asymmetry, dimpling, noticeable scars, granuloma, or transient facial nerve weakness.

The most common complication to rhytidectomy is hematoma formation, with an incidence of up to 15% [103]. Hematomas can be avoided by maintaining perioperative blood pressure below 150/100 mmHg and by holding all anticoagulation therapy prior to surgery and obtaining meticulous hemostasis during surgery [104]. Skin flap necrosis is a less common but more severe complication that occurs in up to 3.6% of procedures [103]. In reconstructive surgery, the most common nerve damaged is the great auricular nerve, leading to numbness of the periauricular area and ear lobe. This can be avoided with careful dissection over the SCM muscle. A more dramatic injury results with damage to the facial nerve. Incidence is 0.1 to 2.6% and

most commonly involves the marginal mandibular and temporal branches. Careful incision planning and conservative flap trimming allows the surgeon to avoid hairline displacement and hypertrophic scars [104].

Eyelids

Signs of aging in the upper third of the face include brow ptosis and the development of deep forehead skin furrows. Loss of skin elasticity combined with weakened muscle tone accentuates these changes [105]. Surgery aims to reduce forehead wrinkles and raise the brow to give a more youthful appearance. Optimal brow position is at or slightly above the orbital rim and in women, arches about two-thirds along its lateral course. There should be a noticeable distance between the brow and the upper eyelid and a visible eyelid cleft. Options to implement these changes include forehead lifting and blepharoplasty.

Five approaches exist for forehead and brow lifting: direct, coronal, mid-forehead, endoscopic, and trans-blepharoplasty [106]. The direct method allows for a long lasting lift but can leave prominent scarring. The coronal approach provides the best exposure but may result in hair loss, paresthesias, and hematomas. The trichophytic modification of the coronal method creates a less obvious scar line. The mid-forehead approach is best for deep wrinkles and allows the entire brow to be sculpted while maintaining the hairline. The endoscopic approach is a newer method and conceals scars while minimizing complications, but requires more meticulous technique. According to a recent systematic review, despite increased technical difficulties there is no evidence supporting endoscopic brow surgery over open brow lifting. Open brow-lift is still an excellent choice, especially in patients with short or normal forehead length and deep wrinkles, with results comparable to endoscopic surgery [107]. Forehead and brow lifting method choice depends on patient expectations, level of the hairline, skin type, and surgeon preference but all allows for a more youthful face and pleasing brow position [108,109].

Signs of aging around the eyes specifically include upper lid redundancy, loss of volume with pseudoherniation of lower eyelid fat, and upper eyebrow ptosis. Upper eyelid skin redundancy and orbicularis oculi hypertrophy is corrected by skin and muscle excision [110-112]. Correction of the baggy eyelid can be completed with a cutaneous or transconjunctival approach for lower lid fixation, often combined with lateral reticular canthopexy. Upper eyebrow ptosis can be managed by forehead lifting, as mentioned above, or with direct browpexy or transblepharoplasty which involve incisions directly above the brow or above the lid. Injection of fat or other fillers can also help increase upper brow volume, helping to create a more youthful appearing eye.

Lips

The lips are a prominent facial structure that shows specific signs of aging. Aged lips are less full, have blunted Cupid’s bow, and an attenuated white roll. Vertical rhytids can also evolve in the upper and lower lids from continued use of the orbicularis muscle [111]. Downward turn of the oral commissures gives a sad or angry “marionette” appearance. Fillers are often used to increase vertical height and increase lip volume, but poor technique or overfilling can result in overt lip projection giving the appearance of a “duck lip.” Surgical options aim to raise the upper lip, increase red:white lip ratio, and correct the downward turn of the oral commissures without the use of fillers. Options include vermilion advancement; V-Y mucosal

advancement, subnasal lift, and corner of the mouth lift [111-113]. Vermillion advancement is performed using an incision along the vermilion border but can result in asymmetry, loss of border definition, and a visible scar, so it is not commonly used. V-Y advancement uses bilateral intraoral incisions and has the benefit of no visible scar but results are unreliable and asymmetry is common. The most commonly used technique is the subnasal lift, in which white lip skin and fascia is resected along vestibule of the nose. Scarring is minimal and asymmetry is less common than the other procedures. The corner of the mouth lift is used to correct the downward turn of oral commissures that may persist through facelift, lip augmentation, or filler use.

Neck

Multiple reconstructive options exist to redefine the aging neck. Goals of these surgeries include defining the mandibular line, enhancing the prominence of the chin, creating a sharper cervicomental angle (of 105-120 degrees), excising excess submental fat, improving platysmal bands, and defining sternocleidomastoid muscles. The goal of these operations is to create the appearance of a thin, long neck. Suspension sutures can also be used to define the mandibular border. Direct skin excision is an option in men with thick lax submental skin who cannot undergo other procedures. Adjuvant procedures can also be performed for enhanced mental prominence such as chin implant or fillers. The primary surgical options are closed liposuction and platysmaplasty [114]. Closed liposuction offers sharper mandibular and SCM borders and should be performed if the skin is distended less than 15%; while over 20% should consider neck lift [114]. A central or submental incision for insertion of tumescence and the liposuction cannula is appropriate. Isolated collections of submental fat may be resected locally instead of through liposuction. As with any cosmetic surgery, common complications include under-correction, hematomas, and seromas. Platysmaplasty offers contouring of the horizontal neck and formation of a deep cervicomental angle while improving platysmal bands and removing pre- or subplatysmal fat. The procedure is often combined with a cervicofacial rhytidectomy and/or liposuction. A submental incision with dissecting and raising of the muscle, skin, or fat superiorly, creates the appearance of a smoother neck with sharper angles. A postauricular incision can also be used to raise excess skin. Complications include excessive tightening or fat removal, recurrence of bands, and palpable sutures.

Lacking Satisfactory Evidence of Anti-Aging Effect

This review of the literature showed a lack of high level evidence for age reversal using microdermabrasion, topical stem cells, pentapeptides (KTTKS), collagen creams, and "oxygen" treatments.

Microdermabrasion

Microdermabrasion is a very popular procedure that can be found in the office of nearly every dermatologist, plastic surgeon, and aesthetician. The American Society for Aesthetic Plastic Surgery alone reported 672,430 procedures performed in 2009 by plastic surgeons and their medical assistants. Microdermabrasion mimics the natural process of exfoliation by mechanically abrading the epidermis with either a diamond tipped wand or a closed-looped system, which blasts fine crystals at the surface of the skin. During this process, only the stratum corneum, which is the outermost layer of the epidermis, is abraded. Between 30-50 passes are required before the stratum

corneum is completely removed [115], however standard practice is to perform only 3 passes per session. Thus, complete removal of the stratum corneum is not achieved with microdermabrasion.

Microdermabrasion claims to treat clinical signs of photo aging, but high-level evidence is lacking in the literature. No long-term effects of microdermabrasion on signs of aging, such as collagen deposition or fine lines, have ever been tested. Additionally, no studies have re-evaluated skin after regrowth of the stratum corneum. One of the only studies to test the effects of microdermabrasion on photo aged skin was performed by Coimbra and colleagues [116]. In this study, 17 subjects were treated with 8 sessions of microdermabrasion at 1-week intervals after which they were assessed on a 5-point scale by a blinded group of both plastic surgeons (N=16) and lay people (N=14). None of the plastic surgeons saw any clinical improvement in fine rhytides, although all evaluators saw mild improvement in hyper pigmentation. Histological analysis of punch biopsies showed increased thickness of the epidermis and increased collagen organization after treatment, which correlates with textural improvement.

There is no evidence that microdermabrasion increases collagen synthesis in the dermis of facial skin unless the coarsest settings and the most aggressive technique are used; however, this aggressive form of treatment also results in more adverse events, such as pinpoint bleeding and bruising [117,118]. The moderately low cost per session is appealing, but the consumer should be aware of the minimal effects of each session, requiring multiple sessions to maintain minimal changes. The regimen suggested to patients is at least 6 treatments on a weekly or biweekly basis followed by touch-ups as needed [118]. When performed at moderate settings, this procedure is safe for all skin types with little risk of post inflammatory hyper pigmentation or scarring. Adverse events include mild erythema and pain lasting 1-2 days. Petechiae lasting one week, abrasions, or urticaria are possible following more aggressive sessions. Ocular complications may occur if crystals enter into the eye, and there is a risk of autoinoculation with viruses such as warts, molluscum contagiosum, or herpes simplex [118]. As multiple sessions are required, the therapy becomes expensive with no evidence that effects are maintained over time.

Topical Stem Cells

While adipose derived stem cells may have an effect on the signs of aging when injected subcutaneously in animal models [119], there is no evidence of a benefit following topical application. It is unlikely that moisturizing creams infused with stem cells result in any added benefit to skin.

Peptides: Topical Growth Factors, Pentapeptide (KTTKS) and Collagen Creams

Growth factors have been reported to increase collagen production in several small, product specific, corporately funded studies lacking a control group [120,121]. It is unclear whether the results of these studies were due to the growth factors alone, the vehicle, or another confounding variable. For example, some creams contained additional active ingredients such as vitamin C (L-ascorbic acid), thus the benefit of the growth factors alone is uncertain. The results of these studies have not been largely reproduced and an explanation for the mechanism of action is still unclear. Growth factors, cytokines, and other proteins are large hydrophilic molecules on a scale of 15,000 Daltons (Da) or larger [120]. Large hydrophilic molecules larger than 500DA are known to have very low penetration through the stratum

corneum [122,123]. Therefore treatments involving large proteins would logically be unable to penetrate the skin to effect change unless the skin was compromised in some way. Because growth factors, such as those derived from fetal fibroblast, have proven to be beneficial for cases in which the outer epidermal layer is lost, such as wound healing and the treatment of burns [124-126], there may be some benefit to using these creams in combination with procedures that interrupt the outer layers of the skin, such as chemical peel or ablative laser therapy. Combination therapy has not yet been studied.

Pentapeptide or KTTKS, a 5 amino acid chain of Lysine, Threonine, Lysine, and Threonine has been popularized recently, but similar to growth factors, this molecule is hydrophilic and has a molecular weight of 563 Da [127], which is too large to penetrate the skin. Penetration enhancers may be a way to overcome this barrier, but the addition of bulky side groups may actually make penetration more difficult. The literature is lacking in well controlled studies of this compound, but one double-blind, placebo-controlled, split-faced study did show a small but significant improvement upon clinical assessment of fine lines and wrinkles with KTTKS cream over a placebo cream after 12 weeks of use [128]. However, because this molecule is not able to penetrate the skin, the effect may be due to some ability to superficially fill in lines and smooth the skin's surface without actually penetrating the epidermis to stimulate collagen or elastin production within the layers of the skin.

For this same reason, topical collagen creams are theoretically ineffective because they are unable to penetrate the outer layer of the epidermis. Thus, topical collagen creams are unable to build upon the skin's own collagen networks.

Oxygen

Some products on the market claim to impart oxygen to the skin. Often, there is no specific ingredient that is identified as the oxygen-bearing compound or that is attributed with the ability to convert toxins into oxygen. This seems to be pure marketing strategy, as no studies have investigated the isolated effects of topical oxygen creams.

Conclusion

Aging is an ongoing intrinsic process, hastened by external factors such as UV exposure and toxins. Signs of aging include a loss of facial volume, thinning of the epidermis and dermis, dyspigmentation, elastosis, and both fine and course wrinkles. Just as factors exist which accelerate aging, interventions also exist to counteract or even reverse the effects of aging. Among the most recommended and clinically effective minimally invasive interventions are sunscreens, antioxidants, retinoids, chemical peels, botulinum toxin, ablative fractional photothermolysis, and photodynamic therapy. Study of other novel therapies such as topical growth factors and peptides, although promising has yet to achieve an adequate level of evidence to substantiate claims or to clarify a mechanism of action when applied topically to intact skin. While popular, micro-dermabrasion provides only fleeting benefits and minimal age-reversal in the long term. Surgical intervention is now often supplemented with fat grafting and neuromodulators. As new anti-aging therapies are developed at an accelerated pace, critical appraisal of clinically proven effects can help guide selection of the most appropriate therapies for each individual's anti-aging needs and desired outcome.

Conflicts of Interest

The authors have no financial interest in any product or piece of equipment discussed in this article.

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