# A Double-Blind Randomized Clinical Trial on the Effectiveness of a Daily Glycolic Acid 5% Formulation in the Treatment of Photoaging

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BACKGROUND. *Low-strength daily formulations of glycolic acid are widely promoted for the treatment of photoaging. However, there are few clinical studies that objectively confirm the benefits of such formulations.*

OBJECTIVE. *The purpose of this study was to determine the effectiveness of a 5% unneutralized formulation of glycolic acid in the treatment of facial and neck photoaging.*

METHODS. *Seventy-five volunteers were recruited to take part in this double-blind randomized placebo-controlled clinical study. Participants applied either the 5% glycolic acid cream or the placebo cream to the face and neck for a period of 3 months. Pre- and posttreatment clinical assessments of photoaging effects were made by the same physician and were analyzed for statistical significance.*

RESULTS. *Overall there were trends towards greater improvement or less worsening in the glycolic acid group for all clinical assessments for photoaging. There was statistically significant improvement favoring the active cream in general skin texture and discoloration. There was a trend favoring glycolic acid in reduction of wrinkles, but this did not achieve statistical significance.*

CONCLUSION. *Unneutralized 5% glycolic acid topical cream when used on a regular daily basis can improve some photoaging effects.* © *1998 by the American Society for Dermatologic Surgery, Inc. Dermatol Surg 1998;24:573–578.*

Glycolic acid formulations have been used for a number of years in the practice of dermatology for the treatment of photodamage, acne, hyperpigmentation, pseudofolliculitis barbae, keratoses, dry skin, and hyperkeratinization.[1–5] Glycolic acid is the smallest of a group of naturally occurring organic acids known as alpha hydroxy acids. When applied topically, glycolic acid has been shown to cause discohesion of keratinocytes and at higher concentrations causes epidermolysis.[6] This action can cause removal of hyperkeratotic lesions and is thought to be the mechanism for improving fine wrinkling caused by photoaging. It has been suggested that glycolic acid may also have a direct effect on dermal components of the skin, including collagen and ground substances.[7] A recent in vitro study has shown that glycolic acid causes an elevated collagen production in fibroblasts.[8] However, there are few well-designed clinical studies verifying the effectiveness of daily applications of topical glycolic acid in concentrations less than 10%.[9] The purpose of this study was to determine the effectiveness of a glycolic acid 5% cream formulation applied daily for the treatment of photoaging.

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## Materials and Methods

### *Patient Selection and Instruction*

Volunteers clinically diagnosed with photoaged skin of the face and neck were recruited to the study. Individuals with a history of tretinoin or glycolic acid use in the past 12 months, pregnancy, any form of dermatitis, or known sensitivity to topical creams were excluded from the study. Informed consent was obtained from all volunteers who were accepted into the study.

Participants in the study were randomized into two groups. Group 1 received the "active" cream containing 5% wt/wt unneutralized glycolic acid (Face First; Cosmetech Pty. Limited, Newcastle, Australia). Group 2 received a placebo cream consisting of the base cream used for the glycolic acid formulation. The study was designed "double-blind" in that neither the participant nor the evaluating physician were aware of which cream the participant was using.

### *Treatment Regimen*

Only the face and neck were treated. Participants were instructed to apply the cream sparingly with a gentle rubbing motion after carefully washing and drying the skin to be treated. For the first week of treatment the cream was applied every second day only. If there was no irritation after 1 week, the participant was instructed to apply the cream daily. If after 2 weeks there was still no irritation, the cream was applied twice daily. This was then continued until the end of the study at 3 months. There were no other changes made to the participant's normal skin care, including the use of sunscreen during the study period. Participants were reviewed


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by the evaluating physician at 6 weeks to determine whether there were any adverse effects and monitor compliance. Final review and evaluation was performed at 3 months.

### *Clinical Evaluation*

The face and neck were evaluated clinically at pretreatment and at 3 months by the physician (AW). The skin was graded according to 10 clinical parameters of photoaged skin:

1. Fine peri-orbital wrinkles (less than 1 mm in width or depth) (FPW);
2. Course peri-orbital wrinkles (greater than 1 mm in width and depth) (CPW);
3. Upper lip wrinkles (ULW);
4. Lower lip wrinkles (LLW);
5. Melasma defined as blotchy, brown, epidermal macules with indistinct margins;
6. Solar lentigines defined as dark brown macules with distinct margins measuring from 3 to 10 mm;
7. Solar keratoses defined as diffuse erythema with keratotic adherent scaling;
8. Guttate hypomelanosis defined as localized macules of absent melanin measuring from 3 to 10 mm in diameter;
9. Poikiloderma defined as a symmetrical reddish-brown pigmentation of the neck, typically sparing the sub-mental area;
10. General skin texture graded from smooth to severe roughness.

A rating of nil (0), mild (1), moderate (2), and severe (3) for each category was made pretreatment and again at 3 months by the same evaluating physician (AW). The physician did not review the notes of his pretreatment evaluation at the time of the 3-month evaluation. Not all participants had all 10 criteria of photodamage but to qualify for inclusion in the study, participants were required to have a score of at least 1 (mild) in at least one of the parameters of photodamage.

### *Statistical Analysis*

All data for physician ratings and patient responses were entered onto a Claris Filemaker II database (Claris Corporation, Santa Clara, CA).

Physician ratings were coded on an ordinal scale with nil = 1, mild = 2, moderate = 3, and severe = 4. In addition to an overall score in which the responses for each of the 10 individual ratings were summed (giving a possible range of 10–40), a wrinkle score and a discoloration score were calculated. These two scores consisted of the sum of four ratings (range, 4–16).

The ratings used for the wrinkle score were: FPW, CPW, ULW, and LLW. The ratings used for the discoloration score were: Melasma, solar lentigines, guttate hypomelanosis, and poikiloderma.

Treatment changes (post minus pre) within the treatment group were assessed using the Wilcoxon signed rank test. The between group comparisons were done with the Wilcoxon two-sample rank sum test. $P$ values of 0.05 or less were considered statistically significant.

## Results

### *Study Population*

Seventy-five volunteers (three male, 72 female) with a mean age of 46.42 years (SD = 10.80), ranging from 29.55 to 69.38 years (median, 45.41) participated. Thirty-nine patients were randomized to active therapy and 36 to placebo. The average duration of therapy was similar in the two groups (Table 1). Four patients withdrew from active therapy and two patients withdrew from placebo therapy, giving a completion rate of 90% and 94% for the two groups, respectively. One participant in the glycolic acid group stopped using the cream after 6 weeks because her skin had become red after increasing the applications to twice daily. She had not experienced any irritation when applying the cream once daily. Four other participants using the active cream reported slight, transient burning or stinging sensations after application. None of the placebo group complained of irritation. One participant from each group reported transient redness after application. One participant using the glycolic acid product withdrew when she elected to have collagen replacement therapy during the study. One participant in each group moved away from the area during the study and the other two volunteers who withdrew from the study (one from each group) were unable to be contacted to determine the reason for their withdrawal.

*Table 1. Patient Age and Duration of Therapy by Treatment Group*

| *Treatment Group* | *Age (Years)* | *Duration of Therapy (Days)* |
|---|---|---|
| Glycolic Acid 5% | (n = 39) | (n = 34) |
| Mean | 46.52 | 88.86 |
| SD | 11.43 | 7.69 |
| Median | 47.20 | 86 |
| Range | (30–69) | (74–117) |
| Placebo | (n = 36) | (n = 36) |
| Mean | 46.30 | 90.41 |
| SD | 10.24 | 10.55 |
| Median | 45.14 | 85 |
| Range | (31–66) | (75–122) |

### *Physician Scores*

#### *Wrinkle Scores*

The wrinkle score for an individual could range from 4 to 16. A score of 4 indicating no wrinkles of any sort and a score of 16 indicating severe wrinkles in all areas. The mean pretreatment wrinkle score was 9.7 (SD = 3.2) in the active group and 9.6 (SD = 3.2) in the placebo group. There was a trend towards improvement (decrease) in wrinkle scores in both treatment groups (active: mean change = −0.34; placebo: mean change = −0.06), however, these changes were not statistically significant and there were no significant differences between the groups (Table 2 and Figure 1).

While there was a statistically significant worsening from baseline in FPW in the placebo group ($P$ = 0.039), there was also a slight worsening of FPW in the active

*Table 2. Descriptive Statistics: Wrinkle Scores*

| | *Pretreatment Sum of Wrinkle Scores* | *Posttreatment Sum of Wrinkle Scores* | *Differences in Wrinkle Scores (Post- Less Pretreatment)* |
|---|---|---|---|
| Glycolic | (n = 39) | (n = 35) | (n = 35) |
| Mean | 9.69 | 9.11 | −0.34 |
| SD | 3.2 | 2.86 | 1.47 |
| Median | 9 | 9 | 0 |
| Range | (5–16) | (5–16) | (−4–3) |
| *P*-value* | — | — | 0.1902 |
| Placebo | (n = 36) | (n = 34) | (n = 34) |
| Mean | 9.58 | 9.53 | −0.06 |
| SD | 3.17 | 2.49 | 1.18 |
| Median | 9 | 9 | 0 |
| Range | (4–15) | (6–14) | (−2–2) |
| *P*-value* | — | — | 0.8265 |
| prob > \|Z\|† | — | — | 0.5526 |

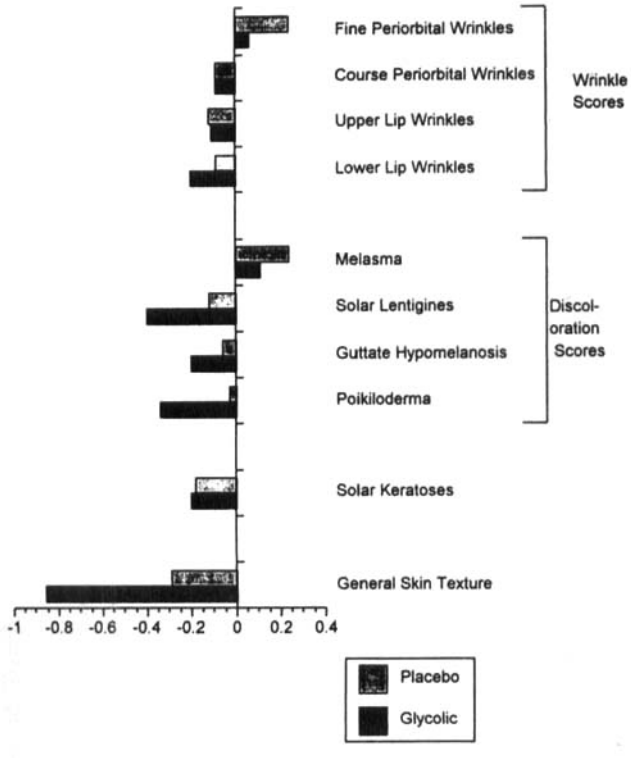
** Wilcoxon signed rank test of change significantly different from zero.*
*† Wilcoxon two sample test comparing active and placebo groups.*

group and there was no statistically significant difference between the two treatment groups (Figure 2). No other wrinkle scores for either group changed significantly during the study.

### *Discoloration Scores*

Discoloration scores were calculated in the same way as wrinkle scores. The mean discoloration score at baseline was similar in the two treatment groups (active:

***Figure 1.*** *Mean changes in sum of wrinkle, discoloration, and total scores (Post-Pre) for patients on glycolic acid and placebo.*



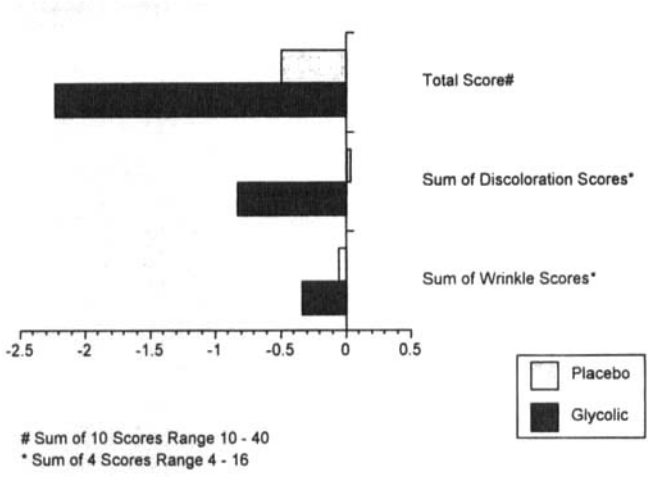




***Figure 2.*** *Mean changes in physician scores (Post-Pre) for patients on glycolic acid and placebo.*

mean = 7.1; placebo: mean = 7.2). There was a statistically significant reduction in the discolouration score in the active treatment group (mean change = −0.83, $P = 0.02$) and no change in the placebo group (mean change = 0.03, $P = 0.9$). A test of the difference in change in the two treatment groups approached statistical significance ($P = 0.05$) (Table 3 and Figure 1).

Melasma worsened significantly in the placebo group, otherwise, there were no statistically significant changes in the placebo group. In the active group there was a highly statistically significant improvement in solar lentigines (mean change = −0.4, $P = 0.0009$) and a significant improvement in poikiloderma (mean change = −0.34, $P = 0.01$). However, there was also some tendency for improvement in the placebo group and the differences between the two groups did not reach statistical significance ($P = 0.08$ for solar lentigines and $P = 0.06$ for poikiloderma) (Figure 2).

*Table 3. Descriptive Statistics: Discoloration Scores*

| | *Pretreatment Sum of Discoloration Scores* | *Posttreatment Sum of Discoloration Scores* | *Differences in Discoloration Scores (Post- Less Pretreatment)* |
|---|---|---|---|
| Glycolic | (n = 39) | (n = 35) | (n = 35) |
| Mean | 7.13 | 6.23 | −0.83 |
| SD | 1.63 | 1.55 | 1.85 |
| Median | 7 | 6 | −1 |
| Range | (5–11) | (4–10) | (−6–2) |
| *P*-value* | — | — | 0.0176 |
| Placebo | (n = 36) | (n = 34) | (n = 34) |
| Mean | 7.22 | 7.21 | 0.03 |
| SD | 1.46 | 1.55 | 1.57 |
| Median | 7 | 7 | 0 |
| Range | (4–15) | (6–14) | (−2–2) |
| *P*-value* | — | — | 0.9136 |
| prob > \|Z\|† | — | — | 0.0521 |

** Wilcoxon signed rank test of change significantly different from zero.*
*† Wilcoxon two sample test comparing active and placebo groups.*

*Table 4. Descriptive Statistics: Total Scores*

| | *Pretreatment Sum of Total Scores* | *Posttreatment Sum of Total Scores* | *Differences in Total Scores (Post- Less Pretreatment)* |
|---|---|---|---|
| Glycolic | (n = 39) | (n = 35) | (n = 35) |
| Mean | 20.82 | 18.17 | −2.23 |
| SD | 4.94 | 3.91 | 3.17 |
| Median | 20 | 17 | −2 |
| Range | (14–33) | (13–26) | (−12–5) |
| *P*-value* | — | — | 0.0001 |
| Placebo | (n = 36) | (n = 34) | (n = 34) |
| Mean | 20.89 | 20.29 | −0.50 |
| SD | 4.62 | 3.74 | 2.51 |
| Median | 20 | 20 | 0 |
| Range | (14–31) | (15–30) | (−5–5) |
| *P*-value* | — | — | 0.2989 |
| prob > \|Z\|† | — | — | 0.0113 |

* *Wilcoxon signed rank test of change significantly different from zero.*
† *Wilcoxon two sample test comparing active and placebo groups.*

### *General Skin Texture, Solar Keratoses, and Total Score*

In addition to the four wrinkle components and the four discoloration components, solar keratoses and general skin texture were also included in the sum of scores. Both groups showed statistically significant reductions in roughness of skin texture (active: mean change = −0.86, $P = 0.0001$, placebo: mean change = −0.29, $P = 0.0046$). There was also a statistically significant difference between the two groups ($P = 0.005$).

Both groups showed statistically significant reduction in severity of solar keratoses (active: mean change = −0.20, $P = 0.03$; placebo: mean change = −0.18, $P = 0.03$) but there was no statistically significant difference between the groups ($P = 1.0000$).

Table 4 and Figure 1 show the descriptive statistics for the sum of all scores giving pretreatment, posttreatment, and the difference from baseline. Individual scores could have ranged from 10 to 40. However, the scores ranged from 14 to 33, with the mean pretreatment score for active treatment being 20.8 (SD = 4.9) and for placebo being 20.9 (SD = 4.6). The active treatment group showed a highly significant difference from baseline (mean change = −2.23, $P = 0.0001$) and there was a statistically significant advantage to active treatment when the two groups were compared ($P = 0.01$) (Figure 2).

## Discussion

This study is the first double-blind, randomized, controlled clinical trial conducted on the use of an unneutralized glycolic acid product of less than 10% concentration for the treatment of photoaged skin. There has been one published double-blind vehicle-controlled

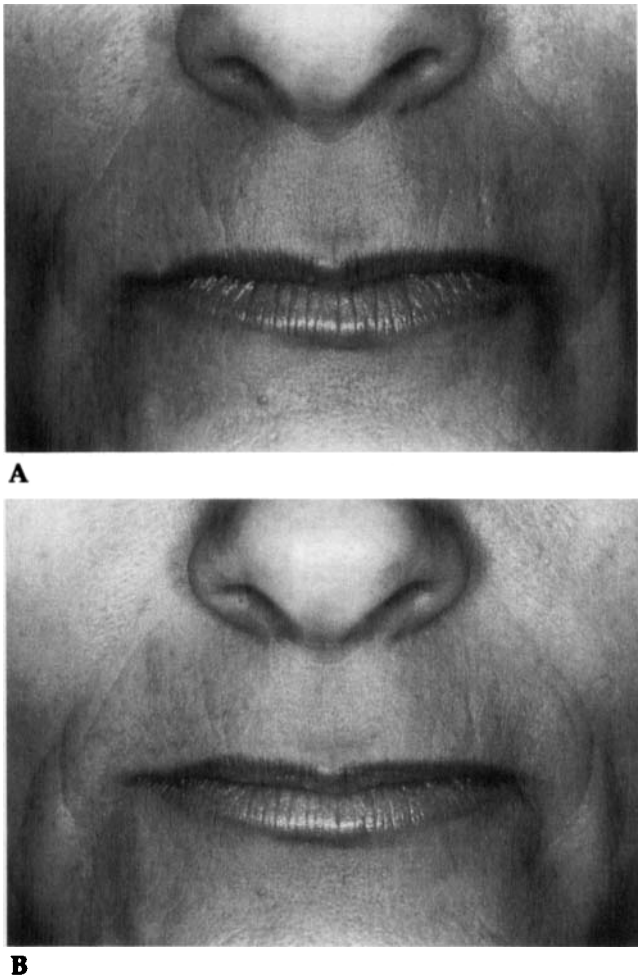
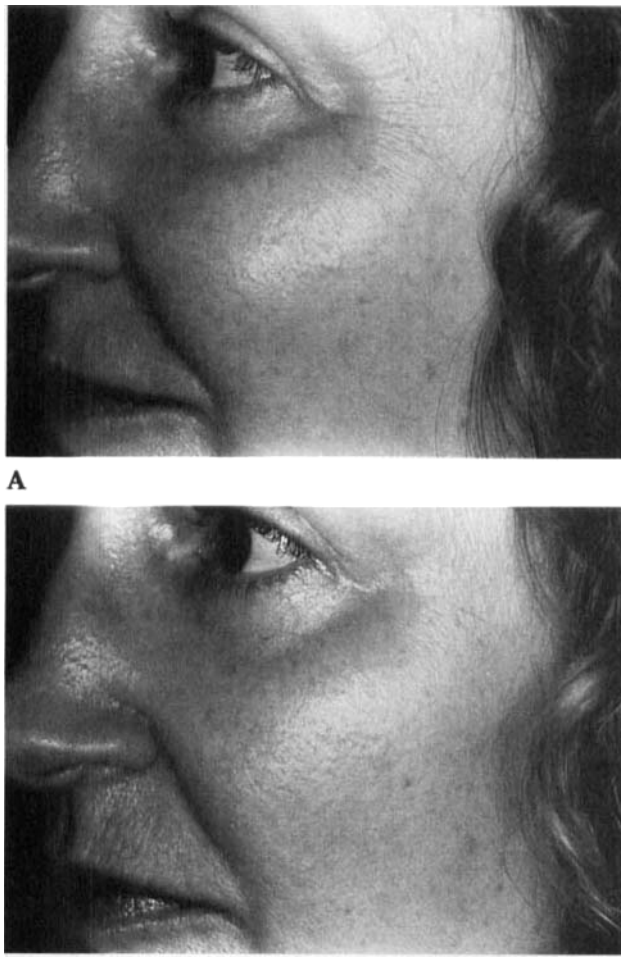



***Figure 3.*** *This 50-year-old patient treated with the active cream had reduction of upper lip wrinkles from moderate (2) to mild (1). A) Before treatment; B) after 3 months.*

study using glycolic acid 50% solution applied topically for 5 minutes to one side of the face, forearms, and hands, once weekly for 4 weeks.[10] This particular study concluded that 50% glycolic acid peels were beneficial in improving rough skin texture, actinic keratoses, and fine wrinkling seen in photoaged skin. In addition, it was reported that solar lentigines were improved although "glycolic acid only had a very mild effect on skin lightening." Course wrinkling remained unchanged and the authors had concluded that this was related to the short duration of the study.

In our study, general skin texture improved with both the active and control groups, but improved considerably more in the glycolic acid group (Figure 3). The effect was quite marked and highly statistically significant. We believe that this effect is caused by thinning of the stratum corneum.[1,10] However, glycolic acid showed no significant effect on wrinkles, fine or course. There was a trend favoring glycolic acid in the total wrinkle score but this did not achieve statistical significance. This may be because there was no effect or



A

B

***Figure 4.*** *This 49-year-old patient treated with the active cream had improvement in general skin texture from slight roughness (1) to smooth (0). This effect is most noticeable on the lateral orbit region. Incidental reduction in fine linear telangiectasias on the central cheek region is also noted. A) Before treatment; B) after 3 months.*

because there was a small effect that required larger numbers of participants to identify or a longer term study (Figure 3).

Glycolic acid significantly reduced the degree of discoloration, particularly solar lentigines and poikiloderma. Lightening of solar lentigines and solar-induced epidermal hypermelanosis may be the result of several factors. First, glycolic acid may remove excessive epidermal pigmentation by increasing the growth of normal, undamaged cells underneath the lesions. In addition, the individual keratinocytes contain fewer melanosomes in a hyperproliferative epidermis.[10] Second, thinning of the stratum corneum will indirectly lighten the skin since each layer of corneocytes contains melanin, which contributes to the color of the skin. It is also possible that glycolic acid may have a direct effect on excessive epidermal pigmentation by inhibiting tyrosinase activity.

To the best of our knowledge, this is the first report of topical glycolic acid improving poikiloderma. While part of this effect is no doubt the result of reduction in epidermal hypermelanosis, it is possible that fine telangiectases may be improved by topical glycolic acid (Figure 4). Braverman and Fonferko[11] have postulated that the microvascular changes seen in photodamaged skin are caused by effects on the veil cell, which is a flat fibroblast-like cell surrounding dermal vessels. A recent in vitro study[8] has demonstrated that glycolic acid stimulates collagen production in fibroblasts. We postulate that the improvement in poikiloderma may in part be caused by similar beneficial effect of glycolic acid on the dermal veil cell. Studies using electron microscopy would be required to confirm this.

Worsening of melasma in the placebo group was most likely related to staging the study in spring with increasing ultraviolet exposure to participants between the pre- and posttreatment assessments.

Overall, there were trends towards greater improvement or less worsening in the glycolic acid group for all clinical assessments for photoaging. Thus, the overall sum of scores showed statistically significant advantage to the glycolic acid group. We conclude that low-strength glycolic acid in the form of a topical cream when used on a regular daily basis can improve some photoaging effects.

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## Commentary

*We do know that glycolic acid preparations at higher percentages from 8% to 70% glycolic acid show improvement in many*

*of the effects of photoaging. There is reversal of some of the skin changes, such as sallowness, roughness, and mottled hyperpigmentation, and fine wrinkling. It is always interesting to see how the effect of lower glycolic acid formulations used over a longer period of time will affect these photoaging changes.*

*This article is a double-blind randomized clinical trial on the effectiveness of a 5% glycolic acid (unneutralized) cream used daily over a 12-week period. It is interesting that 5% glycolic acid cream improved first the mottled hyperpigmentation and the skin texture. The improvement of mottled pigmentation also included poikiloderma of the neck. There were no major effects on wrinkling.*

*Many patients come to the clinician for treatment of their "brown discoloration," whether the color is due to lentigines, poikiloderma, melasma, or postinflammatory hyperpigmentation. To know that even a low 5% glycolic acid cream (unneutralized) can assist in the reversal of some of these changes is very helpful. To improve other aspects of photoaging, such as fine or coarse wrinkling, would probably require higher percentages of the glycolic acid and/or would need a longer duration of therapy.*

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