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Effects of topical DHEA on aging skin: A pilot study

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Abstract

Objectives: Dehydroepiandrosterone (DHEA) is a steroid hormone involved in physiological aging. When administered by oral route, it has been shown to positively affect skin condition on aged people. The purpose of this pilot study was to observe the in vivo effects on skin aging of topical DHEA (1%).
Methods: The DHEA formulation (1%) or the vehicle was topically applied for 4 months to facial and hand skin, in two groups of 20 post-menopausal women. The efficacy of the treatment was evaluated on the basis of clinical and biophysical signs linked to skin aging.
Results: We showed that DHEA treatment increased the rate of sebum, which was perceived rather positively by a menopausal population usually affected with a declining sebum level. Topical DHEA tends to improve skin brightness, to counteract papery appearance of skin and epidermal atrophy, a characteristic feature of hormone-related skin aging. Topical DHEA could also act on skin process related to wrinkles, but this result remains to be confirmed.
Conclusions: This pilot study showed beneficial effects on skin characteristics that are rarely provided by topical treatments. It raised some interesting clues towards the treatment of skin aging.

Keywords: Aging; DHEA; Skin; Topical treatment

1. Introduction

Dehydroepiandrosterone (DHEA) and its sulfate (DHEA-S) are steroids secreted by corticoadrenal glands. They inter-convert freely and continuously via hydroxysteroid sulfotransferases and steroid sulfatase. It has been noted that serum level of DHEA-S was optimum at 25–30 years and then progressively decreased with age [1–3]. This decreasing level in the course of aging tends to suggest that the related steroid could be implicated in physiological aging; DHEA potential to counteract the effects of aging has been approached in several reported studies. However, tests in humans have mainly involved in the study of metabolic parameters in a small number of patients [4–7].

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DHEA is the most abundant steroid in the body and more particularly in the skin [8], which raises the question of its role. However, DHEA has been shown to positively affect skin condition in aged people, when administered by oral route [9]. Improvement of the skin status was observed, particularly in women, in terms of hydration, epidermal thickness, pigmentation and sebum production. Thus it was of major interest to compare the effects of DHEA in menopausal skin when applied topically in a double-blind, placebo-controlled study.

2. Methods

The randomized, double-blind comparative study was carried out in two parallel groups. The study protocol was approved by Marseille (France) Regional Ethics Committee. The study was conducted from January to April.

2.1. Volunteers

The study involved 40 healthy post-menopausal women aged from 55 to 70 years (mean: 60 ± 4 years.). The mean number of years since menopause was 10 ± 6 years. A little more than half of the subjects were under hormone replacement therapy, i.e. estrogen–progestin treatment (10 in the vehicle group, 12 in the DHEA-treated group, the mean number of years on therapy was 5 ± 4 years). Before enrolment, each subject was fully informed of the nature of test product and signed an informed-consent form.

2.2. Study protocol

The volunteers were divided into two groups; one received a cream preparation containing 1% DHEA and the other received the vehicle only, i.e. exactly the same formulation without the active ingredient (DHEA). Applications were made twice a day for 4 months to the face and the back of one hand. The other hand did not receive any treatment and was taken as control. The volunteers had been allocated using a randomization procedure for both the treatment group and the application side. The randomization list was balanced by a group of 10 using the procedure Proc Plan from the SAS statistical software release 8.1.

Each volunteer was left free to apply the preferred amount of cream according to their usual habits. The amount applied was measured at the end of the study by collecting and weighing every tube used. It showed an average use of 2.67 ± 0.2 g/day for the DHEA-treated group and 2.71 ± 0.2 g/day for the vehicle-treated group which corresponds to an average 1.28 mg/cm^2 per application. There was no statistical difference between the two groups as regards the average use of cream ($p > 0.05$).

2.3. Evaluation

The efficacy of the treatment was evaluated at 0 and 4 months, on the basis of clinical and biophysical criteria of skin aging.

2.3.1. Clinical assessment

The same expert clinician performed all of the clinical evaluations, using an ordinal scale graduated from 0 (absent) to 9 (extreme). Wrinkles were assessed on the crow's foot. Fine lines, lentigines and skin brightness were rated on the cheeks using this scale. The back of the hand was used to assess the papery appearance (which we defined as a parchment-like skin [10,11]) and skin brightness, using the same ordinal scale (0–9). Taking all the spots into account on the back of hands, actinic lentigines were also evaluated according to an overall score graduated from 0 to 7, referencing to an in-house validated photographic scale. Global photoaging of the face was assessed using C.E.M. Griffiths photoaging scale [12].

Women's comments on the cosmetic properties of the applied cream and/or unpleasant effects of the product were collected at the end of the study.

2.3.2. Non-invasive assessment

The examination sites for every volunteer were defined on a personal transparent sheet in order to insure an exact repositioning at different exam times.

Sebum production was measured using white adhesive tapes (Sebutape®, CuDerm, TX, USA) which were applied for 20 min onto defatted forehead skin [13]. Lipids absorbed by the tape showed up as transparent spots which were measured using image analysis (Quantiseb®, Monaderm, Monaco). Each spot corresponded to one active sebaceous gland.

Skin thickness was determined using a B-mode ultrasound device developed in our laboratory [14]. A 25-MHz probe (Panametrics) was used to determine full-skin thickness (i.e. epidermis + dermis) using image analysis quantification as described in a previous paper [14]. The field of view was 5 mm (in depth direction) × 15 mm (lateral direction).

Epidermal thickness was measured using a 22-MHz probe (PVDF type) on images with a field of view of 2 mm in depth and 20 mm in the lateral direction. The methodology used for the measurement was extensively described in a previous paper [15].

Ultrasound imaging was performed on the temple (perpendicular to the crow's foot, one centimeter from the eye's corner) and hands (mid-zone of the back of hand).

The level of skin hydration was evaluated in the face (cheek) by measuring electrical capacitance using a Corneometer® (Courage & Khazaka, Cologne, Germany) [16]. Six measurements were recorded on randomly distributed sites and averaged.

Skin color was assessed by chromametry (Chromameter Minolta CR200, Minolta, Osaka, Japan) according to a three-dimensional L, a^*, b^* CIE standard system [17]. L is the luminance axis, a^* the redness axis and b^* the yellowness axis. Six determinations were performed on the face (cheek) and six on each hand, on randomly distributed sites, and the means recorded.

Assessment of crow's foot wrinkles was made using image analysis (Quantirides®, Monaderm, Monaco) on a negative Silflo replica [18]. The number of wrinkles was counted, and their length, depth and developed area were measured and averaged out.

2.4. Statistical methods

The data pertaining to hands were treated by paired analysis, systematically considering the differences between untreated skin and either the DHEA cream-treated or vehicle-treated skin. The quantitative variables were analyzed using repeated measures analysis of variance (SAS MIXED procedure) with the following factors: group (DHEA vs. vehicle), time (M0 vs. M4), and group × time interaction. For the qualitative variables (clinical scores) a method of weighted least-squares type was used (SAS CATMOD procedure), taking into account the factors of group (DHEA/vehicle), time (M0/M4), and group × time interaction. DHEA cream and vehicle at M0 and M4 were compared and the changes between M0 and M4 were tested in the DHEA-treated and vehicle-treated groups. The threshold of significance was set at 0.05 (non-adjusted).

3. Results

Most of the significant observed modifications are listed in Table 1 and detailed below.

3.1. Sebum production

The number of active sebaceous glands (cm^{-2}) increased significantly after 4 months in DHEA-treated group ($p = 0.0001$) whereas no significant change was found in the vehicle-treated group ($p = 0.4$) (Table 1).

3.2. Wrinkles and skin microtopography

The profilometric analysis of crow's foot replicas showed that the mean length of wrinkles significantly evolved in a different way in the two groups (Table 1). The length of wrinkles increased in the vehicle-treated group (+15%, $p = 0.002$) while it kept stable in DHEA-treated group (−3%, $p = 0.53$). At M4, the difference between the two groups shows a statistical trend ($p = 0.06$). The mean wrinkle area evolved following a similar trend. It increased with the vehicle (+25%, $p = 0.01$) while it remained constant in DHEA-treated group (−4%, $p = 0.59$). These two sets of results reflect a worsening of wrinkles in the vehicle group.

Clinically, although the assessment of wrinkles on the whole face evidenced a detectable improvement of the depth of fine lines (of the order of 10%) and wrinkles (of the order of 20%) over the course of time ($p < 0.001$), a similar improvement was observed in the two groups of subjects (Table 1).

3.3. Clinical parameters representative of skin aging: brightness and papery appearance

In DHEA-treated group, skin brightness on the hands tends to be improved ($p = 0.06$) and outshines the vehicle-treated group at M4 ($p = 0.05$).

Table 1
Statistical significance of the differences between groups and evaluation time

	Significance of group × time interaction	DHEA comparison (M0 vs. M4)	Vehicle comparison (M0 vs. M4)
Seborrhea (*n* spots/cm^2)	**0.016**	**0.0001**	0.41
Skin relief (mean length)	**0.008**	0.53	**0.002**[a] (worsening)
Skin relief (mean area)	**0.03**	0.59	**0.013**[a] (worsening)
Skin relief (mean depth)	0.22	0.07	0.95
Skin relief (mean number)	0.16	0.29	0.35
Wrinkle (clinical score)	0.31	**0.002**	**0.0001**
Fine lines (clinical score)	0.65	**0.0001**	**0.0001**
Brightness (face)	0.23	**0.0004**	**0.0001**
Brightness (hand)	0.25	0.060	0.14
Actinic lentigines (face)	0.57	**0.037**	0.24
Actinic lentigines (hand)	0.69	0.14	0.16
Global photoaging	0.53	**0.006**	**0.009**
Color *a*[a] component	0.70	**0.015**	**0.004**
Capacitance	0.71	**0.001**	**0.005**

Statistical significant values.
[a] It corresponds to a worsening of mean surface and length of wrinkles in vehicle-treated group.

On the face, skin brightness evolved favorably in the course of time but similarly in the two groups (Table 1).

Though the group × time interaction was not significant ($p = 0.2$), the papery appearance of skin underwent a significant improvement with DHEA at M4 vs. M0 ($p = 0.015$) while the vehicle did not provide significant change ($p = 0.16$). The difference between the two treated groups was significant at M4 ($p = 0.03$) (Fig. 1).

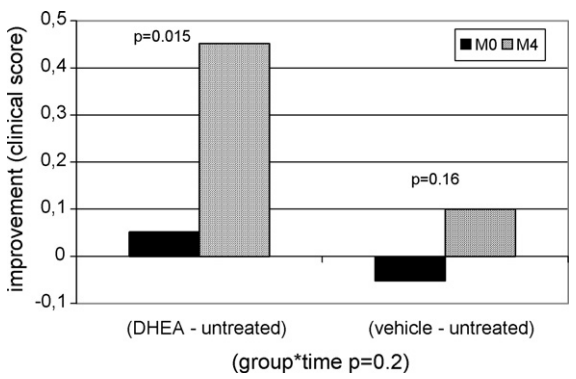

Fig. 1. Improvement in the papery appearance of skin on the back of the hand. Each bar represents the difference between DHEA-treated side (respectively vehicle-treated side) and the controlateral untreated side.

3.4. Thickness of skin and epidermis

Epidermal thickness measured on the face was found to increase by 14% with DHEA cream ($p = 0.0001$) vs. 7% with vehicle ($p = 0.024$) (Fig. 2). Nonetheless, at M4, the difference between the two groups was not statistically significant. On the back of the hand, an epidermal thickening of 7% was recorded in DHEA group (vs. 2% in vehicle group) which is at the limit of significance threshold (each group being paired with untreated hand) at M4 ($p = 0.06$), while at

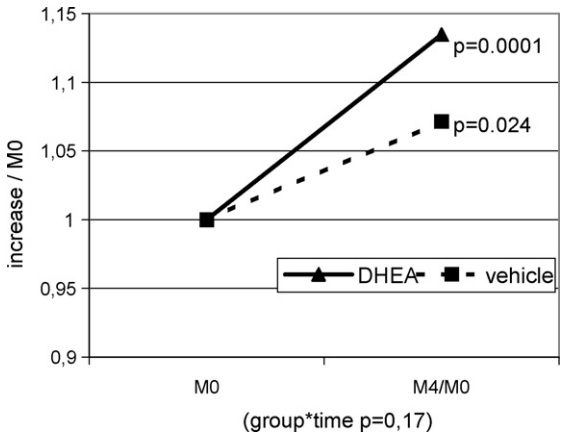

Fig. 2. Epidermal thickness change on the face. Values have been normalized to M0 value for each group.

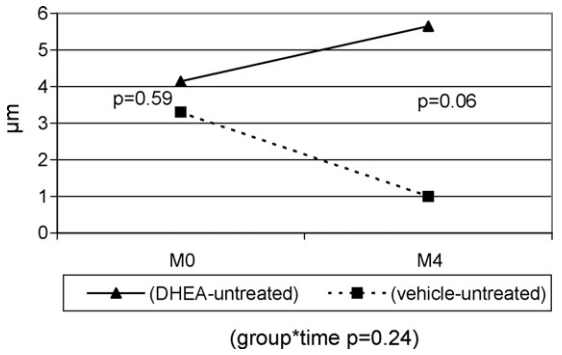

Fig. 3. Epidermal thickness changes on the back-of-the-hand: each point represents the difference between treated hand (respectively DHEA- or vehicle-treated hand) and the controlateral untreated hand.

M0 there was no difference between the two groups ($p = 0.59$) (Fig. 3). Skin thickness did not present any variation during the study ($p > 0.4$).

3.5. Parameters representative of actinic skin aging

Improvements were noticed in facial lentigines over the course of time in the group treated with DHEA ($p = 0.04$) while no significant change was observed in vehicle group ($p = 0.24$), but again the difference between the two groups was not statistically significant at M4 (Table 1). The global score for hand lentigines did not change in the course of the study (Table 1). There was a slight improvement in global photoaging but it was equivalent in the two groups (Table 1).

3.6. Skin color

'a*' component increased significantly by 20–30% ($p < 0.01$) in all groups including untreated skin (Table 1). 'b*' component only tended to decrease in DHEA group on the face ($p = 0.16$) and the variation was not statistically significant on the hands ($p > 0.3$). Skin luminance L* did not show any modification ($p > 0.2$).

3.7. Capacitance

Significant improvements were observed on the face in both groups between M0 and M4 ($p < 0.01$), albeit no difference between the two groups (Table 1).

3.8. Women's comments

Any sign of androgen excess such as body hair growth or greasy skin was not spontaneously reported. Ten weeks after the beginning of the treatment, one woman of the DHEA group presented some lesions of acne which resolved without any complementary treatment, just by reducing the frequency of cream application during the following 2 weeks. The code was not broken for this volunteer.

4. Discussion

To consider the exploratory results obtained in this study, we have to keep in mind the reported skin effects of steroids described in menopausal skin. Although it has been hypothesized since Goldzieher [19] that estrogens have an impact on skin, a lot of controversial results have been published [20–28], which evidences how difficult it is to study the in vivo effects of steroids in skin. The controversial results reported in the literature could be explained by two main factors. The first one is to discriminate specific effects of sexual steroids on skin during aging process. The second one is related to the large variability of menopause-induced consequences in the body between women, in respect to the estrogen supplementation given by the aromatase pathway of DHEA.

Demonstration of topical DHEA on skin needs to consider statistical significant value for group × time interaction, in order to be different from the vehicle effects. It is the case for sebum production. As expected [9] DHEA demonstrates an increasing effect on sebum secretion. Such a result was not estimated as an undesirable effect by the women involved in the study. In fact, DHEA corrected the post-menopausal hypo-seborrhea, with sebum rates returning close to those found in a young adult [29]. Restoring, even partially the sebum component of the hydrophilic film at skin surface should help to provide the skin with an improved protection from drying out. The effect of DHEA on sebaceous glands evidenced an androgenic effect in this skin epidermal target. It clearly showed that DHEA as formulated had a good bioavailability. Although we observed in one woman only some clinical signs of acne (weak, after 3 months), no other androgenic sign, including facial hair growth was observed.

The exploratory purpose of this study allowed us to look at other effects, even if significant value for the group × time interaction is not reached. Some of these effects showed a difference between M4 and M0, which could represent additional potential skin targets for DHEA, but with a lower or a slower impact on skin.

One of the most important and troublesome aging prints is the presence of facial wrinkles. Replica analysis reflected an impairment of skin relief (i.e. an accentuation of wrinkles) in the vehicle group during the 4-month study. The DHEA group did not show such a change suggesting that it could interact with skin process related to wrinkles formation. This could suggest that structural changes observed in microrelief between both groups were not still big enough to have a clinical impact. In addition, a moisturizing effect is a well-known way to improve skin surface including skin brightness and wrinkles [30]. It could explain that, as compared to baseline, there was a similar clinical improvement in wrinkles in both groups. However, structural changes observed in microrelief between both groups suggested that DHEA is likely to have some effects against wrinkle. Additional study must be done to confirm and specify this aspect.

Further effects of DHEA in skin must also be taken into consideration: epidermal thickening, papery appearance of the skin and effects on skin color and lentigines.

The thickening of the epidermis as measured in DHEA group vs. vehicle-treated group deserves attention. This result should not be discounted in view of the absence of a significant difference at M4 between DHEA group and vehicle group, which can be related to the small number of subjects involved in the pilot study. The observed effects of DHEA in counteracting age-linked skin atrophy are of particular interest since epidermal atrophy is a parameter which appears to be directly linked to hormonal aging [31]. DHEA-related thickening cannot be explained merely by SC moisturization, as the variations in thickening and in capacitance are not parallel. Historically, the only active non-hormonal agent available and known to induce such an effect was all-*trans* retinoic acid (0.05%) topically applied for 2 months which we previously reported to induce an epidermal thickening of 5% higher than from vehicle [11]. Although authors evidenced, some decades ago, a significant anti-atrophic effect [19], more recent papers fail to find some significant thickening of the epidermis [21,24]. Most of the efficient hormonal treatment for epidermal atrophy includes some testosterone [19,32,33]. As far as DHEA is concerned, its effect on epidermal atrophy could be related to the recent observations of its metabolism in skin [34]. The authors show that the transformation of exogenous topical DHEA in post-menopausal women skin is preferentially into androgens. So, we could estimate that this anabolic effect is similar to the testosterone effect previously reported.

Any effect on total skin thickness has been observed. In the literature, hormonal treatments which have an impact on total skin thickness were mainly due to some long treatment (6–12 months, sometimes several years) [21,24–26,28]. Moreover, age modification of skin thickness as well as the hormonal supplementation effect on this thickness [22,23] remains a very controversial topic [35]. In our previous study, we did not observe skin atrophy before the age of 70 [14]. All these elements could explain why we did not observe significant changes on total skin thickness with our study design (4-month treatment, mean age 60 years).

DHEA appears to influence papery appearance of the skin, which is particularly relevant for an anti-aging product. This effect could be related to recent findings on DHEA-induced changes of procollagen and of extracellular matrix regulation [36]. In our study, only topical 0.05% all-*trans* retinoic acid has been able to provide such an effect [11]. This result must be considered with attention, knowing that papery aspect is among the main parameters by which individual age is estimated in old people [10].

Results on sebum production, epidermal atrophy and papery skin have to be considered in the light of those observed in a previous study on the effects in skin of orally administered DHEA [9], which induced similar results. However, the effects on the yellow component of skin color (b^* component), observed in the per os study [9] failed to be statistically confirmed here. Only a trend has been observed, probably due to a limited number of volunteers. In this matter, we have to notice the effects observed on facial lentigines which tended to diminish with DHEA. The way by which DHEA could play a role on skin pigmentation stays unknown.

5. Conclusion

DHEA is a buffer hormone whose effects depend on intracrine metabolic pathway determined by target cells. This could explain why DHEA can act both as androgen or estrogen. The effects observed in skin (sebum production and epidermal thickening) could be related to both. As skin aging is a multifactorial process in which steroids could be involved, more specifically in women, DHEA could be of interest in the treatment or the prevention of skin aging. The present study confirmed the potential of topical DHEA as a treatment for skin aging, as it has been previously observed with oral route treatment. Additional studies are needed to confirm these preliminary findings.

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