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ORIGINAL ARTICLE

Effect of a novel dietary supplement on skin aging in post-menopausal women

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Objective: The aim of the present study was to quantify the effects on skin in post-menopausal women of a novel dietary supplement (Imedeen Prime Renewal™) that contained soy extract, fish protein polysaccharides, extracts from white tea, grape seed and tomato, vitamins C and E as well as zinc and chamomile extract.
Design: The study was a 6-month double blind, placebo controlled, randomized study on healthy post-menopausal females.
Setting: The study was performed at a commercial Contract Research Organisation (TJ Stephens & Associates Inc., TX, USA).
Interventions: Two tablets of Imedeen Prime Renewal™ or placebo were given twice daily for 6 months.
Subjects: Thirty-eight (active group) and 42 (placebo group) subjects completed the study out of 100.
Results: Clinical grading showed that the active group had a significantly greater improvement ($P<0.05$) compared to placebo for the face after 6 months treatment for: forehead, periocular and perioral wrinkles, mottled pigmentation, laxity, sagging, under eye dark circles and overall apperance; skin on the décolletage after 2, 3 and 6 months treatment and skin on the hand after 3 and 6 months treatment. Photo evaluation showed that the active group had a significantly greater improvement ($P<0.05$) on the face after 3 and 6 months for several parameters. Ultrasound measurements showed that the active group had a significantly greater improvement ($P<0.0001$) for density measurements after 6 months treatment.
Conclusion: In summary, this novel dietary supplement, Imedeen Prime Renewal™, provides improved condition, structure and firmness of the skin in post-menopausal women after 6 months.
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Keywords: dietary supplementation; clinical study; post-menopause; skin aging; photo aging; imedeen

Introduction

Aging of the skin is the result of intrinsic aging defined as the changes that occur with the passage of time and extrinsic aging by photo damage as defined by the changes in the skin that is for example, induced by the cumulative exposure to ultraviolet light. Other environmental factors such as heat, cold, wind, chemicals, pollution and smoking may contribute to the skin changes imposed on intrinsic aging.

In general, aged skin shows a decrease in epidermal thickness, with a flattening of the dermal–epidermal junction. The dermis decreases in thickness by about 1% per year throughout adult life (Yaar and Gilchrest, 1999). In post-menopausal women skin collagen decreases by about 2% per year (Bolognia, 1995), and decreases in other matrix and cellular components of the skin are also seen. The decline in fibroblast activity coincides with a decrease in the amount of dermal collagen and elastic fibres, as well as a fragmentation of the elastic fibres. Vascular changes associated with aging include vascular fragility which contributes to the atrophy of hair bulbs. Proteoglycans, one of the ground substances in which collagen and elastic fibres are imbedded, decrease in quantity. As proteoglycans bind water 1000 times their own weight, their decline contributes to the decreased turgor of old skin. Thus the biological understanding of aging of the skin has made prevention possible and treatments for example tretinoin and alpha-hydroxy acids (Olsen *et al.*, 1992) more efficient. In addition to topical treatments, dietary consumption of certain plants or fish oil have also been found to modulate the balance of lipid inflammatory

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mediators and are therefore valuable in the treatment of inflammatory skin disorders (Boelsma *et al*., 2001). A food supplement of marine origin has also been found to improve the appearance of photoaged skin (Heule, 1992; Heule, 1994; Sigler and Rasmussen, 2003; Sigler *et al*., 2004) after up to 1 year of treatment with no serious side-effects related to the treatment (Kieffer and Efsen, 1998). The aim of the present study was to quantify the effects on skin of a novel dietary supplement that contained soy extract, fish protein polysaccharides (Kieffer and Efsen, 1998), extracts from white tea, grape seed and tomato, vitamins C and E, zinc gluconate and chamomile extract in post-menopausal women.

Materials and methods

Subjects

One hundred female subjects were enrolled and randomized to treatment with active treatment ($n=50$) or placebo ($n=50$). Drop-outs were not replaced.

Inclusion criteria: healthy females (99 Caucasians, one Hispanic) ranging in age from 45 to 65 year inclusive were enrolled after written informed consent and willingness to follow study requirements. All subjects were 1 to 5 years post-menopausal as determined by a health questionnaire. All subjects had Fitzpatrick Skin Type II–III (Patnak *et al*., 1999), modified Glogau score of II–III (Glogau, 1996) and mild to moderate photodamage on the back of the hands as determined by the clinical grader. Further, the subjects were in good health as determined by a questionnaire, with a body mass index between 20 and 30, smoking maximally 10 cigarettes daily. In addition, the subjects avoided excessive sun exposure and refrained from using tanning beds. The subjects were asked to refrain from facial or hand treatments by physicians or skin care professionals during the course of the study.

Exclusion criteria: skin, mental and uncontrolled metabolic diseases, history of breast cancer, ovarian cancer or any hormone-related disease, gastro-intestinal disease, impaired circulation, allergy or sensitivity to seafood or soy, using prescription drug for improving skin appearance and initiation or change in hormone replacement therapy during the study. Use of any dietary supplements within 1 month of the study start with the indication of improving the appearance or condition of the skin and use of oral vitamins or nutritional supplements equal to more than one daily multivitamin tablet.

There were no differences between the active and the placebo groups (Table 1) with regard to Fitzpatrick and Glogau classification or age (56.8 ± 4.3 vs 56.6 ± 4.7 years, $P>0.05$).

The study was approved by the Integ Review Institutional Review Board, Dallas, Texas, and adhered to current GCP practice regulations. All subjects gave signed informed consent after written information and a possibility for further questioning.

Design

The study was performed as a 6-month double blind, placebo-controlled randomized clinical study and performed at a commercial Contract Research Organisation (TJ Stephens & Associates Inc., TX, USA), where both subjects and the investigator were blinded to the study randomization. Sponsor was Ferrosan A/S, Soeborg, Denmark.

During a wash-out period of 28 days, all subjects replaced their usual moisturizer and cleanser with supplied standardized products (Purpose® Liquid Cleansing Wash and Purpose® Dual Treatment Moisture Lotion SPF 15) and were used throughout the study period.

The active ingredients per daily intake (two tablets in the morning and two tablets in the evening) of the dietary supplement (Imedeen Prime Renewal™, Ferrosan A/S, Soeborg, Denmark.) comprised 350.0 mg soy extract (10% soy isoflavones) (Solgen 10, Solbar Plant Extracts, Israel), 210.0 mg Bio marine complex consisting of fish protein polysaccharides (Kieffer and Efsen, 1998), ViTea ™188.7 mg: white tea extract (*Camellia sinensis*) 62.4 mg (White tea extract, 40% polyphenols, China National Chemical construction Anhui Company), grape seed extract (*Vitis vinifera* L.) 27.5 mg (Vitis vinifera seeds dry extract/ Lycopene (Alextan®), Indena spa, Italy), tomato extract (*Lycopersicum aesculentum*) 28.8 mg[4], vitamin C (sodium ascorbate 99% TG) 60 mg (Sodium ascorbate 99% TG, DSM Nutritional Products, Switzerland), vitamin E (d-α-tocopheryl acetate) 10.0 mg (Vitamin E 700, ADM Nutraceuticals, The Netherlands), zinc (zinc gluconate) 5.0 mg (Gluconal® ZN, Glucona BV, The Netherlands) and

Table 1 Subject groups' assignment to Fitzpatrick skin, modified Glogau classifications and mean age

		Active group (n = 38)		*Placebo group (n = 42)*	
		Number of subjects	*Percentage of subjects*	*Number of subjects*	*Percentage of subjects*
Fitzpatrick skin classification	II	8	21.11%[a]	11	26.61%
	III	30	78.95%[a]	31	73.81%
Modified Glogau classification	II	20	52.63%[a]	15	35.71%
	III	18	47.37%[a]	27	64.29%
Mean age (years) ± s.d.		55.76 ± 4.34[a]		56.61 ± 4.65	

[a]Active group not significantly different from the placebo group ($P>0.05$).

chamomile extract (*Matricaria recutita* L.) 100 mg (only included in the evening tablets) (Matricaria dry hydro alcoholic extract >0.75%, Bernett, Italy).

The placebo tablet ingredients comprised per daily intake (two tablets in the morning and two tablets in the evening) commercial grade 1115 mg maltodextrin, 266 mg starch, 95.8 mg burnt sugar, 30.4 mg silicon dioxide, 11.4 mg magnesium stearate and 0.76 mg riboflavin.

Active and placebo tablets were manufactured by Ferrosan A/S, Soeborg, Denmark according to GMP guidelines.

All subjects were examined at seven visits: screening (visit 1), baseline (visit 2), 2 months (visit 3), 3 months (visit 4), 4 months (visit 5), 5 months (visit 6), 6 months (visit 7). The wash-out period of 28 days was between visits 1 and 2.

At visits 1–6, subjects underwent the following procedures: weight measurement (BMI calculated), compliance check by tablet count and tablet supply for the next period (except visit 7).

At visit 2–4 and 7, subjects underwent the following assessments: clinical grading, digital photography for blinded evaluation, ultrasound measurements, moisturization measurements, elasticity measurements and self-assessment questionnaire.

Approximately 1 week after baseline (visit 2), all subjects were contacted by telephone to ensure compliance.

Before objective skin measurements, the subjects rested for at least 30 min in a room with standardized temperature between 61–72°F and humidity conditions between 31 and 50%.

Assessments

Clinical grading. Clinical grading of skin on the face, décolletage and hand was carried out by one examinator on a 0–9 scale with 0.5. intervals where 0–3 was mild, 3–6 was moderate and 6–9 was severe as described previously (Rizer *et al*., 1999).

Parameters evaluated included:

Face: forehead wrinkles, wrinkles of periocular area, perioral wrinkles, mottled hyperpigmentation, tactile roughness, laxity, sagging, teleangiectasia, under eye dark circles and overall facial appearance.

Décolletage (chest): crepyness, mottled hyperpigmentation and overall appearance.

Hand: crepyness, thinness and mottled hyperpigmentation. Triplicate pinch recoil measurements were performed on the back of the qualified hand to assess skin elasticity/resiliency as described previously (Rizer *et al*., 1999; Barkovic *et al*., 2000).

Photo evaluation. Two visible light digital photographs were taken as follows:

- Full-face: top of the forehead to the bottom of the chin at a 45° angle to show the selected side of the face as qualified by the investigator.
- Full-face plus décolletage.

A Nikon D100 digital camera body and a Nikkor AF 70–180 mm Micro NIKKOR lens attachment was used for all photography. Digital images were recorded using Nikon Capture software and were saved to a computer as Nikon Raw files. The same photographic equipment was used at each study visit.

Digital photographs were graded for severity of forehead wrinkles, periocular wrinkles, perioral wrinkles, mottled hyperpigmentation, teleangiectasia, under eye dark circles and overall appearance using the same scales as described for clinical grading (Rizer *et al*., 1999).

Ultrasound measurements. A DUBplus 20 (Taberna, Pro Medicum, AG, USA) Ultrasound unit was used to measure skin density (Altmeyer *et al*., 1992) as a B scan of selected crow's foot area (adjacent to the corner of the outer eye) as qualified by the investigator. The system used a standard 20 MHz transducer with a focal distance of 12 mm and 40 dB amplification. The measurements were taken with the probe oriented perpendicular to the body axis while the subjects lay supine. Analysis of ultrasound images included measurement of combined epidermal and dermal thickness.

Other skin measurements included moisturization (NOVA dermal Phase meter 9003, NOVA Technology Corporation, USA) (Rizer *et al*., 1999), skin elasticity (Cutometer SEM 575, Courage and Khazaka, Germany) (Berndt and Elsner, 2001) as well as self-assessment questionnaire (Rizer *et al*., 1999).

Statistics. Analysis of variance (ANOVA) was used to compare differences between the active and the placebo treatments. Significance level was set to $P \leqslant 0.05$. Values are presented as means ± s.e.m. Mean values for clinical grading and instrumentation measurements at Month 2, Month 3 and Month 6 were statistically compared to mean baseline values using a paired *t*-test at the $P \leqslant 0.05$ significance level. Incidence of improvement was calculated for each attribute. Comparisons were made between the active group and the placebo group using a two sample *t*-test for independent data at the $P \leqslant 0.05$ significance level.

Results

Thirty-eight female subjects in the active group and 42 female subjects in the placebo group completed the study.

Twenty subjects were discontinued from study participation: seven from the active group and three from the placebo due to schedule conflict/unable to attend visit(s), four from the active group and five from the placebo group due to non-compliance/ineligibility to protocol specifications and one from the active group due to adverse event (swollen tongue, probably related to intake of active group study treatment).

The results of clinical grading, evaluation of digital photographic images and ultrasound measurements are given in Tables 2 and 3 respectively.

Table 2 Clinical grading values of face, hand and décolletage in post-menopausal women before and after supplementation with dietary supplement or placebo for 2, 3 and 6 months

	Active group (n = *38*)				*Placebo group* (n = *42*)				
	Baseline	*Month 2*	*Month 3*	*Month 6*	*Baseline*	*Month 2*	*Month 3*	*Month 6*	*ANOVA P-value*[a]
Face									
Forehead wrinkles	4.4±0.3[b]	4.3±0.3	4.1±0.3	4.0±0.3	4.7±0.4	4.6±0.4	4.5±0.3	4.6±0.3	0.01[c]
Periocular wrinkles	5.4±0.2	5.0±0.2	4.7±0.2	4.6±0.2	5.4±0.2	5.1±0.2	4.8±0.2	4.9±0.2	0.02[c]
Perioral fine wrinkles	5.1±0.3	5.0±0.3	4.7±0.3	4.5±0.3	5.2±0.3	5.1±0.2	4.9±0.3	4.9±0.3	0.01[c]
Mottled hyper pigmentation	4.6±0.2	4.4±0.2	4.1±0.2	3.9±0.2	4.8±0.2	4.6±0.2	4.4±0.2	4.4±0.2	<0.01[c]
Tactile roughness	2.2±0.2	1.2±0.2	0.7±0.1	0.5±0.1	2.8±0.2	1.7±0.2	1.1±0.2	1.1±0.2	NS
Laxity	4.9±0.2	4.8±0.2	4.2±0.2	4.0±0.2	4.8±0.2	4.7±0.2	4.3±0.2	4.2±0.2	0.01[c]
Sagging	4.8±0.2	4.7±0.2	4.4±0.2	4.2±0.2	4.9±0.2	4.9±0.2	4.6±0.2	4.6±0.2	0.01[c]
Teleangiectasia	2.7±0.3	2.6±0.3	2.4±0.3	2.3±0.2	3.6±0.3	3.6±0.3	3.4±0.3	3.4±0.3	NS
Under eye dark circles	2.6±0.2	2.4±0.2	2.1±0.2	2.1±0.2	2.5±0.2	2.4±0.2	2.3±0.2	2.3±0.2	0.01[c]
Overall facial appearance	5.3±0.2	5.1±0.2	4.8±0.2	4.5±0.2	5.5±0.2	5.2±0.2	5.0±0.2	5.1±0.2	<0.01[c]
Decollétage									
Crepyness	3.7±0.2	3.6±0.2[d]	3.4±0.2[d]	3.4±0.2	3.7±0.1	3.7±0.2	3.7±0.2	3.7±0.2	<0.01[c]
Mottled hyper pigmentation	5.0±0.2	4.9±0.2	4.6±0.2	4.6±0.2	5.1±0.2	5.0±0.2	4.8±0.2	4.9±0.2	NS
Overall appearance	5.0±0.2	4.9±0.2	4.6±0.2[d]	4.5±0.2	5.0±0.2	5.0±0.2	4.9±0.2	5.0±0.2	<0.01[c]
Hand									
Crepyness	4.9±0.2	4.6±0.3	4.1±0.3[d]	4.0±0.3	5.4±0.3	5.2±0.3	4.9±0.3	4.9±0.3	<0.01[c]
Thinnness	4.4±0.3	4.2±0.3	3.9±0.3	3.8±0.3	4.6±0.4	4.5±0.3	4.3±0.3	4.3±0.3	NS
Mottled hyper pigmentation	4.7±0.2	4.0±0.3	3.4±0.3[d]	3.3±0.3	4.9±0.3	4.4±0.3	4.0±0.3	3.9±0.3	NS
Pinch recoil	2.6±0.1	2.4±0.1	2.3±0.1	2.1±0.1	2.8±0.1	2.6±0.1	2.3±0.1	2.4±0.1	NS

[a]Difference in change between groups, Student's *t*-test (unpaired *t*-test).
[b]Mean values±s.e.m.
[c]Significant difference between active group and placebo at month 6.
[d]Significant difference between active group and placebo ($P<0.05$).

Table 3 Ultrasound density of crow's foot area and grading values of digital photographic images of face in post-menopausal women before and after supplementation with dietary supplement or placebo for 2, 3 and 6 months

	Active group (n = *38*)				*Placebo group* (n = *42*)				
	Baseline	*Month 2*	*Month 3*	*Month 6*	*Baseline*	*Month 2*	*Month 3*	*Month 6*	*ANOVA P-value*[a]
Face									
Forehead wrinkles	4.2±0.2[b]	4.1±0.3	3.9±0.2[c]	3.9±0.2	4.2±0.2	4.2±0.2	4.1±0.2	4.2±0.2	<0.01[d]
Periocular wrinkles	5.0±0.2	4.8±0.2	4.5±0.2	4.4±0.2	5.0±0.2	4.9±0.2	4.8±0.2	4.8±0.2	<0.01[d]
Perioral fine wrinkles	5.0±0.3	4.9±0.3	4.8±0.3	4.9±0.3	4.9±0.2	4.9±0.2	4.7±0.2	4.8±0.2	NS
Mottled hyper pigmentation	4.5±0.2	4.3±0.2	4.1±0.2[c]	3.9±0.2	4.7±0.2	4.6±0.2	4.4±0.2	4.5±0.2	<0.01[d]
Teleangiectasia	1.0±0.3	0.9±0.2	0.9±0.2	0.7±0.2	1.6±0.3	1.4±0.3	1.5±0.3	1.5±0.3	NS
Under eye dark circles	2.4±0.3	2.3±0.3	2.2±0.3[c]	2.2±0.3	2.8±0.3	2.7±0.3	2.8±0.3	2.7±0.3	NS
Overall appearance	5.5±0.1	5.2±0.1	4.9±0.1[c]	4.9±0.2	5.7±0.2	5.5±0.1	5.4±0.2	5.4±0.2	<0.01[d]
Crow's foot area									
Ultra sound density	41.7±1.1	44.5±1.0	45.8±1.0	49.9±1.0	40.7±0.8	44.2±0.8	46.7±0.9	44.1±0.8	<0.01[d]

[a]Significant difference between active group and placebo at month 6.
[b]Mean values±s.e.m.
[c]Significant difference between active group and placebo ($P<0.05$).
[d]Significant difference between active group and placebo at month 6.

Clinical grading showed significant differences between the two treatment groups for the following parameters given in Table 2:

- face forehead wrinkles, periocular wrinkles, perioral wrinkles, mottled hyperpigmentation, laxity, sagging, under eye dark circles and overall appearance (month 6),
- décolletage crepyness (months 2, 3 and 6) and overall appearance (months 3 and 6),
- hand crepyness (months 3 and 6), mottled hyper pigmentation (month 3).

Evaluation of digital photographic images showed significant differences between the two treatment groups for the

following parameters given in Table 3: forehead wrinkles, periocular wrinkles, mottled hyperpigmentation, overall appearance (months 3 and 6), under eye dark circles (month 3).

Ultrasound measurements of dermal density, showed significant difference between the two treatment groups at month 6 as seen in Table 3.

The other skin measurements including moisturization, elasticity measurements and self-assessment questionnaire showed no statistically differences between the active and placebo treated group (data not shown).

Discussion

To our knowledge, this is the first double blind, placebo controlled study showing that a novel dietary supplement is effective in improving the appearance and condition of the skin in post-menopausal women.

Aging of skin affects all individuals and is influenced by genetic, hormonal and environmental factors. For women particularly in the post-menopausal years, acceleration of chronologic aging is enhanced by the loss of estrogen, which causes a rapid loss of collagen during the first 5 years after menopause (Brincat *et al*., 1983; Brincat *et al*., 1985; Brincat *et al*., 1987; Brincat, 2000). It is assumed that phytoestrogens such as soy isoflavones may mimic the effects of estrogen in skin and reduce skin changes in postmenopausal women. ViTea™ was developed by testing the effectiveness of various combinations of antioxidants on cultured fibroblasts. This combination of ingredients may act by reducing the free radical induced damage from oxidative reactions in the skin (Smit *et al*., 2004). The Biomarine complex has previously been shown to have an effect on the quality, structure and appearance of photoaged skin (Heule, 1992; Heule, 1994; Kieffer and Efsen, 1998). *In vitro* studies suggest that deposition of collagen fibres in the dermis is one possible action (Lacroix, 2004, personal communication) although a detailed mode of action is not known.

The ultrasound skin density improvements seen in the present study is supported by investigations in a three dimensional skin equivalent model where a stimulated deposition of collagen type1, increased fibrillin 1 m-RNA, and increased keratinocyte proliferation could be demonstrated from Imedeen Prime Renewal™ ingredients (Lacroix S, 2004, personal communication). It is of importance to notice that ultrasound measurements on the face required 6 months of treatment to be of a magnitude that was measurable. This suggests that long term treatment is required to obtain changes in the skin by dietary supplements.

This placebo controlled study includes both quantitative and qualitative measurements, the majority showing significant improvements after the active treatment. In view of the small size of the study and the variations in the measurements, it is likely that a larger and an extended study period would result in significant improvement also in these parameters.

In conclusion, this novel dietary supplementation with soy extract, fish protein polysaccharides, extracts from white tea, grape seed and tomato, vitamins C and E, zinc gluconate and chamomile extract is effective in improving the appearance and condition of skin in post-menopausal women by objective and significant improvements to skin on face, décolletage and hand compared with placebo.

Thus there is both clinical and mechanistic evidence that such supplementation provides improved structure and firmness of the skin in post-menopausal women.

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