A Randomized, Double-blind, Placebo-controlled, Multi-center, Extension Trial Evaluating the Efficacy of a New Oral Supplement in Women with Self-perceived Thinning Hair

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ABSTRACT

Objective: The purpose of this six-month, randomized, double-blind, multi-center, placebo-controlled study was to determine if the administration of a new oral supplement will promote terminal hair growth. **Design:** A randomized, double-blind study. **Setting:** Two private practices (dermatology and facial plastics). **Participants:** Women 21 to 75 years of age with self-perceived thinning hair. **Measurements:** The primary efficacy endpoint was the change in terminal and vellus hairs in a 4cm^2 target area of the scalp after 90 and 180 days of treatment. Secondary endpoints were change in hair diameter and responses to Quality of Life and Self-Assessment questionnaires. **Results:** Subjects treated with the new oral supplement achieved a significant increase in the number of baseline terminal hairs at 90 and 180 days (for each, $p<0.0001$, respectively) and were significantly greater then placebo ($p<0.0001$). Treatment with the new oral supplement was also associated with a significant increase in baseline terminal hair diameter after 90 ($p=0.006$) and 180 days of treatment ($p=0.001$) which was significantly greater than placebo at the end of the study ($p=0.003$). Improvements in hair growth and hair diameter were associated with significant improvement in most responses to Self-Assessment and Quality of Life Questionnaire responses. There were no adverse events. **Conclusion:** The daily administration of a new oral supplement was associated with significant increases in the number of terminal and vellus hairs and hair diameter. Most study participants believed the use of the oral supplement resulted in significant improvement in skin and hair quality and quality of life. (*J Clin Aesthet Dermatol.* 2015;8(12):15–21.)

As physicians, we may look at a patient and think she has no problem with hair thinning or hair loss, but she may feel very strongly that her hair is thinning. Hair loss in women can appear as early as in their 20s, and with environmental stress, internal stress, multiple medications, and dietary insufficiencies, can often progress. While androgenetic alopecia is a common cause of male pattern hair loss in men and a less common cause of female pattern hair loss in women,[1] this study is not one of androgenetic alopecia. Among women, hair loss is more likely to be due to medications,[2] nutritional deficiency,[3] and physiological or emotional stresses, such as illness or childbirth.[2,4–7] Hair loss and decreased hair fiber thickness are reasons for many older women becoming dissatisfied with their hair[8] and for many, hair loss may be associated with symptoms of depression[9] and diminished quality of life.[10] The authors wanted to determine if patients with self-perceived thinning hair due to daily life stressors (not a specific trigger inducing hair loss as seen with telogen effluvium), nutritional insufficiency (fast food, poor diet), and aging (again not androgenetic alopecia with retention of frontal hair line or central part of scalp) would truly benefit from a new all natural, oral supplement.

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The product containing proteins and glycosaminoglycans of marine origin and other natural compounds has been developed for the treatment of androgenetic alopecia (Viviscal® Hair Nourishment System, Lifes2good, Inc., Chicago, Illinois). This product does not contain hormones, drugs, or industry by-products but it provides essential nutrients to nourish hair naturally. Two 8- and 12-month open-label studies[11,12] have demonstrated the efficacy of this product for the treatment of alopecia in men. The results of the authors' recent pilot study, published in *The Journal of Clinical and Aesthetic Dermatology* in November 2012, showed that the oral supplement was also effective in women with thinning hair due to poor diet, stress, hormonal influences, or abnormal menstrual cycles.[13] Subjects enrolled in that study achieved a significant increase in the number of terminal hairs among Viviscal-treated subjects after 90 and 180 days of daily treatment. In addition, significantly more Viviscal-treated subjects perceived improvements in overall hair volume, scalp coverage, thickness of hair body, hair shine, skin moisture retention, and skin smoothness after 180 days.

Further studies are also being conducted to establish the molecular mechanism by which the new oral supplement promotes hair growth. While the exact mechanism of this product is unknown, some of the preliminary data from early *in vitro* studies have shown that the polysaccharide complexes in it have greater bioavailability when compared with similar products (unpublished results). In addition, this new product has been shown to enhance the proliferation of dermal papillae (DP) cells. DP cells have been shown to play an important role in orchestrating the hair growth cycle.[14,15] Initial studies have shown that this new supplement increases alkaline phosphatase (AP) levels in DP cells (unpublished results). AP is a key marker of the anagen phase; therefore, an increase in its expression suggests an increase in the quantity of DP cells that are actively growing during the anagen phase.[15–17] Thus, *in vitro* examination of the molecular mechanism of Viviscal is consistent with the results of the existing Viviscal clinical studies, where daily intake promotes existing hair growth.

A new professional strength supplement has been specifically designed to promote hair growth in women suffering from temporary thinning hair (New Viviscal® Professional Strength Oral Tablets, Lifes2good, Inc., Chicago, Illinois). The purpose of this multi-center randomized, double-blind, placebo-controlled study was to test the hypothesis that the administration of a new oral supplement for 180 days will promote the growth of terminal hairs and increase hair diameter in a larger group of adult women with self-perceived thinning hair, adding the factor of hair diameter changes due to the product in our evaluation.

METHODS

Study subjects. Women 21 to 75 years of age with self-perceived thinning hair associated with poor diet, stress, hormone influences, or abnormal menstrual cycle, but otherwise healthy with Fitzpatrick skin types I to IV were eligible for enrollment at two clinical trial sites (one dermatology practice and one facial plastics practice). Each subject expressed her willingness to follow study procedures, including maintaining her normal hair shampooing and color treatment frequency and not substantially changing her current diet, medications, or exercise routines for the duration of the study.

Reasons for exclusion from study participation included a history of intolerance or allergy to fish, seafood, or acerola; known allergy or sensitivity to any shampoo or conditioner; a stressful incident within the last six months, such as a death in family or miscarriage (thus patients with severe life stressor suggesting telogen effluvium were excluded); recently (<6 months) started the use of hormones for birth control or hormone replacement therapy; use of other therapies for hair growth, such as light therapy or minoxidil within the last three months; use of medications known to affect the hair growth cycle within the last six months, such as hormone-based contraceptives, cyproterone acetate, aldactone/spironolactone, finasteride, or other 5-alpha-reductase inhibitors; self-reported active hepatitis, immune deficiency, human immunodeficiency virus, or autoimmune disease; self-reported uncontrolled diseases, such as diabetes or hypertension; an active dermatologic condition that might place the subject at risk or interfere with the objectives of the study; other hair loss disorders, such as alopecia areata, scarring alopecia, androgenetic alopecia (determined by clinical exam, patient and family history), and telogen effluvium; participating in any clinical research study; or nursing, pregnant, or planning to become pregnant during the study.

Test material. Subjects were randomized in double-blind fashion to receive the new oral supplement (New Viviscal® Professional Strength Oral Tablets) or placebo. The key ingredients in this product are AminoMar C™ marine complex, a form of silica derived from *Equisetum sp.* (horsetail), vitamin C derived from acerola cherry, Procyanidin B-2 (apple extract powder), L-cystine, and L-methionine. AminoMar C™ comprises a proprietary blend of shark powder and mollusk powder, which are derived from sustainable marine sources. The placebo treatment consisted of inert tablets with similar appearance.

Study procedures. Subjects were instructed to take one tablet of their assigned treatment twice daily in the morning and evening following a meal. Subjects were instructed to maintain their normal hair care routine and use the same brand/type of hair care products and maintain the same haircut, color, and style for the study duration.

This study consisted of a baseline clinic visit and follow-up visits after 90 and 180 days of treatment. A basic physical examination was performed at all three visits, which included a basic body systems overview, vital signs, and scalp examination to rule out any confounding scalp conditions.

During the baseline visit, an approximately 2x2cm ($4cm^2$) target area was selected along the frontalis bone where frontal hairline and lateral hairline meet (hairline junction). A three-point location was recorded based on

TABLE 1. Changes in hair growth and hair diameter

VIVISCAL	BASELINE	DAY 90	DAY 180	SIGNIFICANCE*
Mean terminal hairs (SD), N=17	189.88 (15.24)	297.35 (96.09)	341.00 (60.92)	$p<0.0001$
Mean vellus hairs (SD), N=17	19.94 (1.71)	20.18 (5.40)	22.82 (2.29)	$p=0.0001$**
Mean hair diameter, mm (SD), N=17	0.060 (0.0070)	0.066 (0.0085)	0.067 (0.0085)	$p=0.006$
PLACEBO	**BASELINE**	**DAY 90**	**DAY 180**	**SIGNIFICANCE***
Mean terminal hairs (SD), N=19	190.26 (20.69)	189.21 (19.89)	192.68 (24.11)	p=NS
Mean vellus hairs (SD), N=19	21.79 (5.37)	22.21 (6.71)	22.47 (6.42)	p=NS
Mean hair diameter, mm (SD), N=19	0.061 (0.0092)	0.060 (0.0092)	0.061 (0.0114)	p=NS

*Repeated measures ANOVA across study days contrasts per treatment group; NS=not significant. **Baseline versus 180 days only.

measurements obtained from the medial canthus, lateral canthus, and preauricular skin pit to the hairline junction. Where these three points meet (anterior lateral triangle of scalp), a target area 1cm posterior into scalp hair was chosen. The 4cm^2 target area was marked using a black fine-tip skin marker, such that the three-point triangulation mark was in the center.

Digital images were obtained of the scalp target area at each visit (Canon SD 4500 IS or Nikon D90 with a 105mm Macro Nikor lens). Macrophotographs of the selected target area were also obtained (Nikon Coolpix 4300 camera with a 3GEN Dermlite Foto37 system or Nikon D90 camera with a Nikon 105mm macro lens).

At the baseline visit, 10 terminal hairs in the target area, marked with permanent marker for hair photos, were randomly chosen throughout the target area and cut at the surface of the scalp such that no bald patches were created. Dino-Lite Microscopic digital photographs were used to measure the diameter of the selected hairs at a point 1mm from the cut end of the hair. This procedure was repeated at the 90- and 180-day visits. Subjects completed the Quality of Life and Self-Assessment Questionnaires at the 90- and 180-day evaluation visits.

Study endpoints. Efficacy was assessed by changes in the number of terminal and vellus hairs in the target area of the scalp using phototrichogram analysis at the end of the 180-day study period. Terminal hair is defined as coarse hair, short or long, found on the scalp with minimum cross-sectional diameter of 40µM or greater. Vellus hair is defined as fine, short hairs found on the scalp with maximum cross-sectional diameter of less than 40µM.

The secondary endpoints were changes in terminal hair diameter and responses to Quality of Life and Self-Assessment Questionnaires.

Safety. Safety measures included changes in physical examinations, scalp condition, and vital signs. Subjects were queried about potential adverse events at each clinical visit. Any spontaneously reported adverse events at other times during the study were also recorded.

Statistical analysis. Descriptive statistics were obtained for all variables. Tests of normality of continuous measures were made and data were examined for homogeneity of variance. Changes in baseline hair growth, hair diameter, Quality of Life and Self-Assessment Questionnaire responses were tested using analyses of variance (ANOVA) with repeated measurements. All statistical tests were two-tailed. Differences were considered statistically significant at the level of p-value of ≤0.05 was obtained.

Ethics. This study protocol was approved by a commercial institutional review board (IRB Company Inc., Buena Park, California). Each subject provided informed consent prior to participating in any study-related activity. This study strictly adhered to all applicable guidelines for the protection of human subjects for research as outlined in the United States FDA 21 CFR Part 50, in accordance with the accepted standards for Good Clinical Practices and the standard practices of Ablon Skin Institute Research Center and DeNova Research.

RESULTS

Subject enrollment. The study enrolled 40 adult female subjects with a mean (SD) age of 50.2 years (12.5 years) (range, 25–66 years): 20 were randomized to the new oral supplement, 17 of which completed the study, and 20 were randomized to placebo, 19 of which completed the study. The race/ethnicity of the 36 subjects completing the study were Caucasian (N=28; 70%), Hispanic (N=5; 12.5%), and Asian (N=3; 7.5%).

Primary endpoint. The primary endpoint was the

TABLE 2. Self-assessment questionnaire results					
	VIVISCAL, N=17		PLACEBO, N=19		
Quality	Day 90	Day 180	Day 90	Day 180	Significance*
1. Overall hair volume	4.76 (0.75)	6.12 (0.99)	4.11 (0.57)	4.84 (0.90)	p=0.056
2. Scalp coverage	4.76 (1.03)	6.12 (0.99)	4.21 (0.79)	4.74 (0.93)	p=0.008
3. Thickness of hair body	4.84 (0.81)	5.35 (1.06)	4.37 (0.68)	4.95 (0.91)	p=NS
4. Softness of hair body	4.29 (0.59)	4.94 (1.03)	4.42 (0.61)	4.63 (0.96)	p=NS
5. Hair shine	4.94 (1.03)	5.47 (1.13)	4.21 (0.79)	4.53 (0.77)	p=NS
6. Hair strength	5.00 (0.87)	5.88 (1.11)	4.68 (0.95)	4.95 (0.91)	p=0.019
7. Nail strength	5.12 (1.05)	5.88 (1.11)	4.89 (1.05)	4.79 (1.03)	p=0.030
8. Nail growth rate	5.47 (1.07)	5.94 (1.14)	5.00 (1.00)	4.95 (1.08)	p=NS
9. Growth of eyebrow hair	5.00 (0.87)	5.18 (1.13)	4.32 (0.67)	4.58 (0.90)	p=NS
10. Growth of eyelashes	4.47 (1.28)	5.24 (1.03)	4.42 (0.77)	4.42 (0.90)	p=0.086
11. Skin smoothness	4.65 (0.79)	5.24 (1.15)	4.42 (0.77)	4.58 (0.84)	p=0.074
12. Overall skin health	4.76 (0.83)	5.29 (1.11)	4.47 (0.91)	4.47 (0.84)	p=0.069

*Repeated measures ANOVA; two-way interaction of group by days; N=not significant.

change in hair counts within the 4cm^2 target area using phototrichogram analysis at the end of the 180-day study period. The two groups were significantly different across study days in the number of terminal hairs ($f_{(2,68)}$=48.7, p<0.0001). Among the new oral supplement-treated subjects, there was a significant increase in the number of terminal hairs between baseline and 90 and 180 days ($f_{(1,16)}$=24.36, p<0.0001, $f_{(1,16)}$=129.85, p<0.0001, respectively). There was also a significant increase in the number of baseline vellus hairs, but only at 180 days ($f_{(1,16)}$= 26.35, p<0.0001) (Table 1). There was no significant change in either terminal or vellus hairs among the placebo-treated subjects.

Secondary endpoints. The two groups were also significantly different in terminal hair diameter ($f_{(2,76)}$=6.11, p=0.003). There was a significant increase in terminal hair diameter among the new oral supplement-treated subjects between baseline and 90 and 180 days ($f_{(1,19)}$=9.35, p=0.006, $f_{(1,19)}$=14.13, p=0.001, respectively) (Table 1), but not among the placebo-treated subjects. Responses to the self-assessment questionnaire at 90 and 180 days are summarized in Table 2. Among the new oral supplement-treated subjects, there were improvements seen on 10 out of 12 (83%) of the self-assesment questionnaire over placebo, and three posed assesments showed statistically significant improvement over placebo (3/12 or 25%). The responses to the Quality of Life Questionnaire are summarized in Table 3. There was a significant improvement in 9 of the 13 questions (69%) among the oral supplement-treated subjects versus none for placebo-treated subjects.

DISCUSSION

The results of this study confirm the results of the previous study,[13] which showed the administration of the new oral supplement was associated with significant improvements in the number of terminal and vellus hairs after 180 days of treatment. In addition, it demonstrated a significant increase in the diameter of terminal hairs. Among the subjects completing the trial, the mean number of terminal hairs and vellus hairs increased substantially after 90 days and continued increasing until 180 days while there was no change among placebo-treated subjects. Since the number of terminal and vellus hairs continued to increase between 90 and 180 days, additional improvements in the number of terminal and vellus hairs

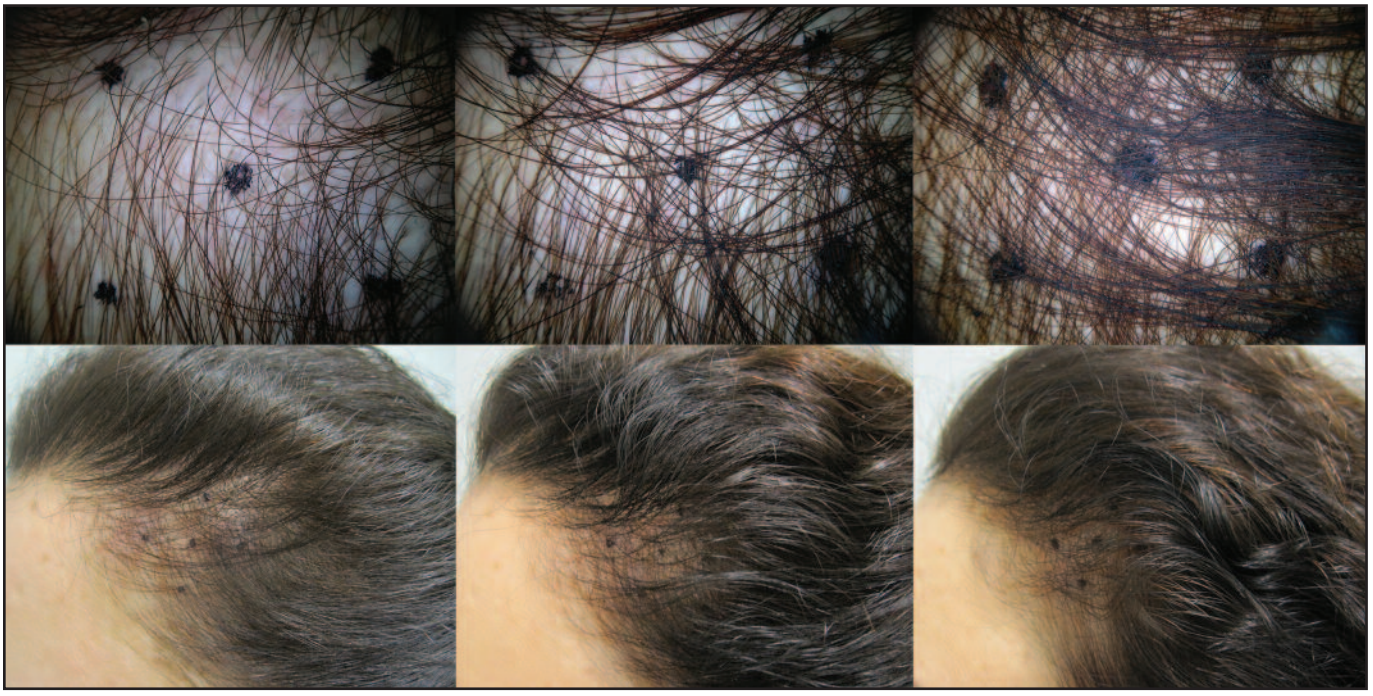

Figure 1. Changes in hair growth, Patient 1. Top Row. Macrophotographs of the selected target area at baseline (left), 90 days (center), and 180 days (right). Bottom row. Digital images of the selected target area at baseline (left), 90 days (center), and 180 days (right).

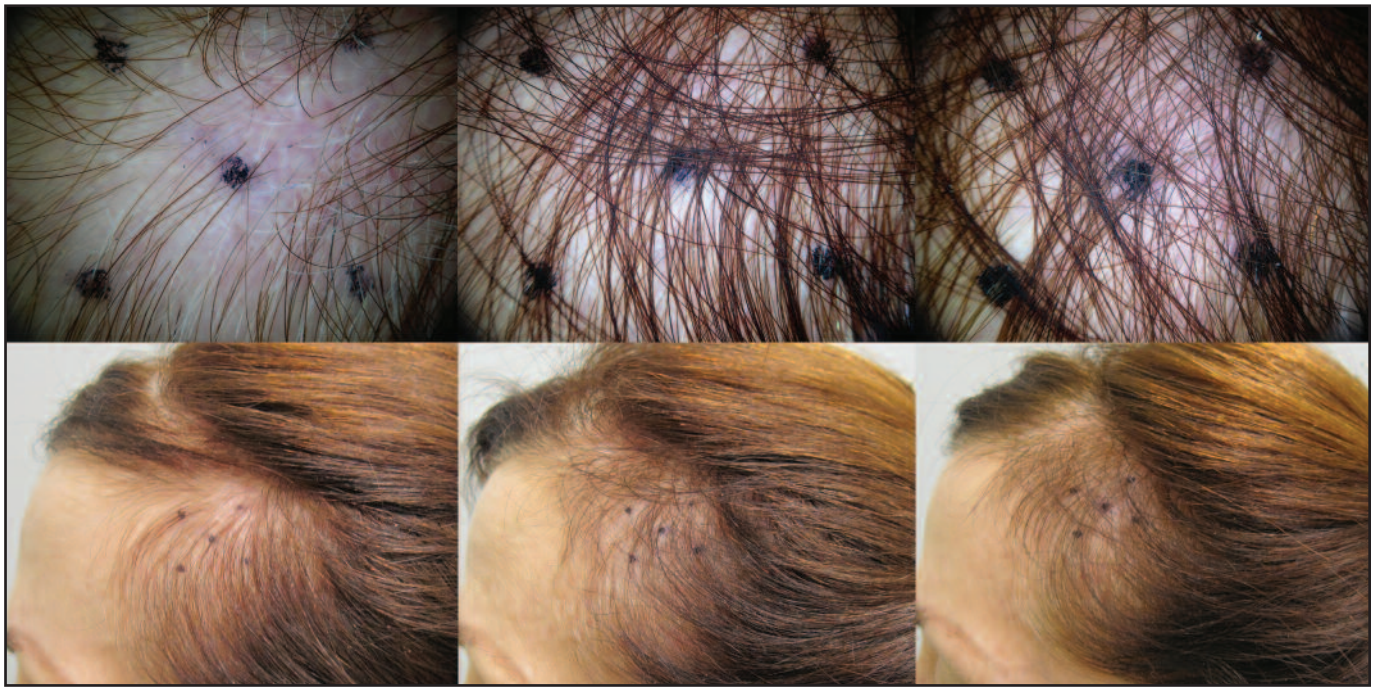

Figure 2. Changes in hair growth, Patient 2. Top Row. Macrophotographs of the selected target area at baseline (left), 90 days (center), and 180 days (right). Bottom row. Digital images of the selected target area at baseline (left), 90 days (center), and 180 days (right).

might also occur if treatment with the new oral supplement were continued beyond 180 days. Future studies should continue to monitor changes in the number of terminal and vellus hairs beyond 180 days. In addition, the current study expands those results to include significant increases in hair diameter. Mean (SD) hair diameter increased from 0.060mm (0.0070mm) at baseline to 0.066mm (0.0085mm) at 90 days and continued to increase reaching 0.067 (0.0085mm) at 180 days.

Among the 12 items in the Self-Assessment Questionnaire, there were significant improvements in seven, including overall hair volume, scalp coverage, hair

TABLE 3. Quality of Life Questionnaire results

	VIVISCAL				PLACEBO			
Question	**Baseline**	**Day 90**	**Day 180**	**Signif.***	**Baseline**	**Day 90**	**Day 180**	**Signif.***
1. I am embarrassed by my thinning hair.	3.00 (0.94)	2.59 (1.12)	1.94 (1.20)	$p<0.0001$	3.21 (0.86)	2.84 (.83)	2.42 (0.84)	p=NS
2. Because of my thinning hair, I avoid social gatherings.	1.47 (0.72)	1.29 (0.69)	1.12 (0.78)	p=NS	1.68 (0.75)	1.74 (0.73)	1.63 (0.60)	p=NS
3. I don't like meeting new people as I feel they are judging me because of my thinning hair.	1.76 (0.83)	1.12 (0.78)	1.18 (0.73)	p=0.010	1.79 (0.86)	1.63 (0.60)	1.74 (0.73)	p=0.030**
4. I avoid going out during the day because of my thinning hair.	1.29 (0.69)	1.24 (0.66)	1.18 (0.88)	p=NS	1.58 (0.84)	1.58 (0.69)	1.37 (0.68)	p=NS
5. My condition impacts my emotional state at work.	1.65 (0.86)	1.53 (1.01)	1.35 (0.93)	p=NS	1.79 (1.18)	2.00 (0.94)	1.63 (1.07)	p=NS
6. I feel my thinning hair has impacted my ability to succeed in interviews.	1.41 (1.06)	1.18 (1.13)	1.00 (0.94)	p=0.068	1.74 (1.15)	1.89 (1.05)	1.53 (1.12)	p=NS
7. My condition has prevented my participation in a sports activity.	1.41 (1.06)	1.47 (0.94)	1.12 (0.93)	p=NS	1.63 (1.21)	1.47 (0.96)	1.42 (0.84)	p=NS
8. My condition impacts my self-esteem.	3.00 (1.12)	2.53 (1.13)	2.00 (1.17)	$p<0.0001$	2.84 (1.21)	2.68 (0.95)	2.11 (0.86)	p=NS
9. My condition makes me feel self-conscious about my thinning hair.	3.06 (0.83)	2.82 (0.95)	2.24 (1.09)	p=0.001	3.16 (0.83)	3.05 (1.03)	2.58 (1.26)	p=NS
10. Because of my thinning hair, I fear being the center of attention.	2.00 (0.79)	1.71 (0.99)	1.41 (1.06)	p=0.053	1.79 (1.08)	1.84 (1.07)	1.74 (1.05)	p=NS
11. I feel my thinning hair is affecting my personal relationships.	2.18 (1.13)	1.59 (1.06)	1.59 (1.06)	p=0.050	1.79 (1.08)	1.79 (0.92)	1.58 (0.77)	p=NS
12. Because of my thinning hair, I am less outgoing than I would like to be.	2.24 (1.20)	1.94 (1.20)	1.59 (1.18)	p=0.045	1.95 (1.08)	1.95 (1.03)	1.84 (0.69)	p=NS
13. Because of my thinning hair, I feel unattractive.	2.82 (1.24)	2.47 (1.18)	1.94 (1.09)	p=0.001	2.89 (0.81)	2.47 (0.91)	2.47 (0.61)	p=NS

***Repeated measures ANOVA; **negative significance; NS=not significant.**

strength, nail strength, eyelash growth, skin smoothness, and overall skin health. This represents an improvement over only four Self-Assessment responses in the previous study.[13] Among the 13 items in the Questionnaire, there were significant improvement in five areas, which indicate improvements in feelings of embarrassment, self-esteem, self-consciousness, and attractiveness.

The results of a recent study showed that Caucasian women perceive decreased hair quantity beginning in the middle of the fifth decade of life, which is not solely due to either loss in hair quantity or hair diameter, but a combination of the two.[8] They found that scalp hair diameter increases between the ages of 20 to about 45 years, then decreases. In contrast, hair density was highest among women 20 to 30 years of age and decreased thereafter with increasing rate. These investigators propose creating "hair amount" as a new metric for the perception of hair loss. Relative scalp hair coverage is the total of all hair cross-sectional areas in $1cm^2$ of scalp surface expressed as μm^2 hair surface per μm^2 scalp surface. Among women with no self-perception of hair loss, the "hair amount" values were virtually the same from ages 25 through 45 years. Only when both diameter and density begin decreasing together in the mid-40s do relative hair amount and a woman's perception of the loss in amount of hair become noticeable. Among women with self-perceived hair loss, the rate of decreasing hair density is significantly faster than for women with no self-perception of hair loss. Since the new oral supplement

increases both hair density and hair diameter, the "hair amount" may be a useful metric for future studies.

CONCLUSION

The twice-daily administration of New Viviscal Professional Strength Oral Tablets was associated with a significant increase in the number of terminal and vellus hairs and in also increased hair diameter in women with self-perceived thinning hair compared to baseline values in this group and to those taking the placebo. Most study participants believed the use of the new oral supplement produced significant improvement in skin and hair quality and quality of life.

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