# A pilot study evaluating the efficacy of topically applied niacin derivatives for treatment of female pattern alopecia

**Zoe Diana Draelos,[1] Elaine L. Jacobson,[2,3] Hyuntae Kim,[2] Moonsun Kim[2] & Myron K Jacobson[2,3]**

[1]*Department of Dermatology, Wake Forest University School of Medicine, NC*
[2]*Department of Pharmacology and Toxicology, University of Arizona, AZ*
[3]*Arizona Cancer Center, University of Arizona, AZ*

## Summary

*Background* Female pattern alopecia is a common dermatologic condition that manifests after puberty. The only approved drug treatment for this condition is 2% minoxidil for topical application.
*Aims* This pilot study examined the effect of topical application of two niacin derivatives, octyl nicotinate and tetradecyl nicotinate, on hair fullness in female alopecia.
*Patients/methods* Sixty female subjects with Ludwig types I–III female pattern hair loss were evaluated in a double-blinded, placebo-controlled (40 active, 20 placebo) design using standardized 35-mm photographic analyses for assessment of efficacy after 6 months of application.
*Results* The niacin derivatives demonstrated a statistically significant increase in hair fullness ($P = 0.04$ compared to the placebo).
*Conclusion* Whereas evaluation of hair growth in women is challenging, this 6-month pilot study demonstrated statistically significant increase in hair fullness on blinded 35-mm photographic analysis. Long-term topical application of nicotinic acid derivatives offers promise for providing benefit in female alopecia and warrants further study.

*Keywords*: female pattern alopecia, niacin, niacin derivatives, topical delivery

## Introduction

Female pattern hair loss (alopecia) affects approximately 20 million women. The condition appears to be familial; however, the exact inheritance pattern is unknown. Hair loss begins at puberty and progresses throughout life. Early detection of the condition is difficult, which is unfortunate, as early diagnosis and treatment are important in achieving optimal therapy. Hair thinning in women usually spares the anterior hairline with a generalized decrease in hair count noted over the entire top of the scalp. However, there are many variations of this hair loss pattern, which seem to be hormonally mediated. A good indicator of female pattern hair loss is a widening part line or a thinning ponytail. Typically, daily hair loss counts do not exceed 100–125 hairs; however, hair follicles that enter the telogen phase do not reenter the anagen growth phase, resulting in a slow net loss of active follicles. The treatment options for this condition are limited and include hair transplants, hormonal supplementation, and minoxidil, a drug that affects calcium homeostasis.[1] Topical 2% minoxidil, available over the counter, is the only approved drug therapy for this condition.

Limited treatment options available for female alopecia has led to the search for other agents that can provide benefit for this condition. A potential candidate for hair growth promotion is niacin (nicotinic acid), in which studies have identified several possible mechanisms of benefit.

Correspondence: Zoe Diana Draelos, MD, 2444 North Main Street, High Point, North Carolina, 27262, E-mail: zdraelos@northstate.net

*Accepted for publication August 4, 2005*

The major bioactive form of niacin, nicotinamide adenine dinucleotide (NAD), plays a central role in cellular energy metabolism and, as a rapidly proliferating tissue, the hair follicle has a high energy requirement.[2] NAD is also the substrate for enzymes involved in the maintenance of genomic integrity[3] and calcium homeostasis.[4] Additionally, skin has been shown to contain niacin receptors that stimulate leptin release,[5] and downstream regulators in the leptin pathway are involved in skin homeostasis[6] and hair follicle cycling.[7] Whereas either niacin or its other vitamin form, niacinamide, has the potential to be converted to NAD, the nicotinic acid receptor responds only to niacin.[8]

Although niacin has the potential to provide benefit to skin and scalp, delivery of niacin per se is not feasible in appreciable amounts as it causes intense vasodilation at the site of application and its physical properties do not allow it to achieve a prolonged residence time in the skin. This has led to the development of myristyl nicotinate, a niacin derivative that effects delivery to skin cells without vasodilation and creates a residence time, allowing conversion to NAD[9] and stimulation of the nicotinic acid receptor in skin cells.[8] Myristyl nicotinate has been shown to promote epidermal differentiation, leading to a strong enhancement of skin barrier integrity.[10] A second niacin derivative, octyl nicotinate, stimulates blood flow with the expected result of enhanced nutrient delivery to the scalp and increased removal rate for metabolic end products. Thus, the potential of myristyl nicotinate and octyl nicotinate to provide benefit to the hair follicle by multiple mechanisms combined with the well-established safety profile of niacin provided the rationale to clinically assess these niacin derivatives in improving hair fullness in women with Ludwig types I–III female pattern hair loss.

## Materials and methods

Sixty female subjects, ages 20–80, who completed an informed consent procedure with Ludwig types I–III female pattern hair loss[11] were enrolled in a 6-month pilot study using a double-blinded, placebo-controlled design. Subjects were assigned randomly to the placebo (20, vehicle only) or active groups (40, vehicle containing 0.5% octyl nicotinate, and 5.0% myristyl nicotinate). Dispensed products were packaged in identical containers. Trisiloxane and dimethicone were major components of the formulation. Because the actives are vitamin-derived substances, both the placebo and the active preparations studied are classified as cosmetics under the current Food and Drug Administration guidelines.

At baseline, subjects were dispensed a 1-month supply of assigned study product. The first dose was applied by a study nurse at the research center. Subjects were instructed to apply once daily at night six metered drops to the scalp in the following manner: one drop each to the right anterior scalp, left anterior scalp, right middle top of the head, left middle top of the head, right posterior scalp, and left posterior scalp. If the hair was washed, the study medication was applied following hair washing. All subjects were supplied with shampoo (Pantene formula for damaged hair, Procter & Gamble, Cincinnati, OH). The frequency of hair washing was self-selected. Subjects were asked to maintain the entry style, color, and curl of their hair throughout the study.

Subjects returned at monthly intervals for evaluation of increased hair fullness, scalp irritation, or other adverse events and product dispensing. They were asked to shampoo the morning of study visit and to avoid applying styling products. Subjects were also asked to assess the appearance of their hair. Standardized photography was used for the assessment of hair fullness, as increases in hair fullness over the 6-month study period are normally not detectable by either the investigator or the subjects. At baseline, month 3, and month 6, Polaroid images were captured of the scalp vertex, with the hair combed away from the vertex like the spokes of the wheel, and the central partline, with the hair combed smoothly to both sides of the head. These images were taken in duplicate with one set provided to the subjects for personal comparison, and the second set remained at the study center. Standardized 35-mm photography was conducted at baseline, 2, 4, and 6 months as follows: vertex view with hair combed away from the crown, superior view with hair parted in midline, frontal view with headband to reveal the anterior hairline. The images were taken with the subject's head in a three-point mount specially designed for hair loss photography (Canfield Scientific). Evaluation was completed on the 6-month photographs as this represents a minimal time to detect changes in hair fullness.

## Results and discussion

Of the total subjects enrolled in the study, 32 of 40 active and 12 of 20 placebo subjects completed the study. A relatively high withdrawal rate is typical for hair fullness/growth studies, but it is interesting to note that proportionally twice as many subjects in the placebo group compared to the active group withdrew in this study. Overall tolerability of the topical formulations was very good. There were no serious adverse events reported, and the mild adverse events included 9 reports of scalp

**Table 1** Evaluation of nicotinic acid derivatives on female pattern alopecia.

| Group | No of subjects | Scoring of hair growth number of subjects (% of total) | | | *P* value‡ |
|---|---|---|---|---|---|
| | | Decrease | No change | Increase | |
| Placebo | 20* (12†) | 1 (8%) | 7 (59%) | 4 (33%) | – |
| Active§ | 40* (32†) | 2 (6%) | 8 (25%) | 22 (69%) | 0·04 |

*Number of subjects enrolled in study.
†Number of subjects who completed the study.
‡Active compared to placebo for one-tailed Mann–Whitney test.
§Active contained 0.5% octyl nicotinate and 5.0% tetradecyl nicotinate.

stinging, 2 of scalp burning, 12 of scalp itching, 4 reporting scalp redness, and 7 reports of eye irritation. These events occurred in both placebo and active groups, indicating that the volatile vehicle and not the active was the source of the irritation.

The study yielded investigator, subject, and photographic assessments. Polaroid photos and subject assessments revealed a positive trend, but did not reach significance at a *P* value of 0.05, which was not unexpected for a 6-month study. The key assessment was based on the standardized 35-mm photographs that were evaluated by a blinded investigator for assessment of improvement in hair fullness. Each set of images was rated on a scale of −1 for decreased hair fullness, 0 for no change, or +1 for increased hair fullness. These data are summarized in Table 1. The data comparing the placebo and active groups demonstrate an increased benefit for the active group with a *P* value of 0.04 as analyzed by the one-tailed Mann–Whitney test for nonparametric data. The placebo effect observed in this study is not uncommon for hair fullness studies. An example of the effect of nicotinic acid derivatives on thinning hair as documented by 35-mm photography at baseline and 6 months of application is shown in Fig. 1.

To our knowledge, this study represents the first attempt to evaluate the effects of niacin derivatives in women with Ludwig stages I–III female pattern hair loss. Female hair fullness studies are difficult to conduct because maintaining a constant hair appearance is challenging and judgements of improved growth are difficult based on hair length. Furthermore, it is not feasible to use many standardized male hair loss assessment techniques in female subjects such as shaving a 1–2-cm area of the scalp and utilizing macrophotography at monthly intervals to obtain hair counts because it is very difficult to recruit female subjects willing to allow this assessment. For this reason, this study used standardized photography to assess improvements in hair fullness.

Although this study indicates that use of niacin derivatives offers promise for providing benefit to individuals with female pattern alopecia, several questions were not

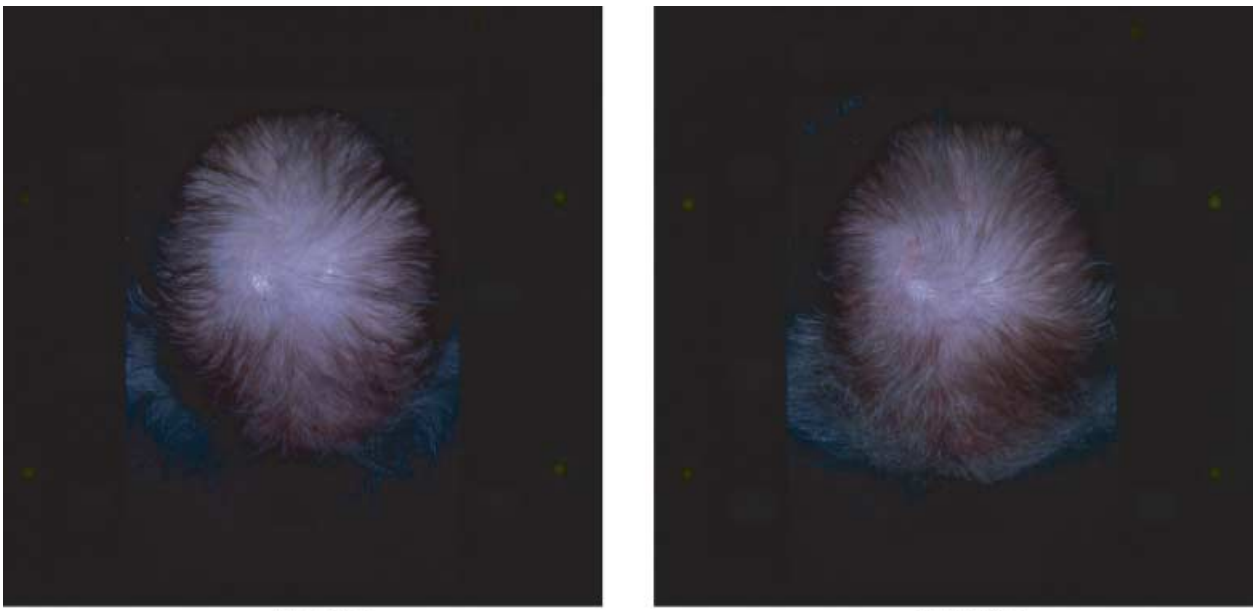


**Figure 1** An example of the effect of nicotinic acid derivatives on thinning hair as documented by 35-mm photography at baseline and 6 months of application.

  

answered by the present study. It was not possible to determine in this study whether the increased hair fullness was the result of increasing the density of active hair follicles or increasing the quality of the existing hair shafts. Additionally, it was not possible to determine in this study whether the benefit was provided by octyl nicotinate, myristyl nicotinate, or a combination of the two niacin derivatives. An extended study will be needed to answer these questions. Because female pattern hair loss is a prevalent problem with few treatment options, further research regarding benefit of niacin derivatives in this condition is warranted.

## Acknowledgements

This research was supported in part by NIH grant R43CA90085 and a grant from Niadyne Inc. MKJ and ELJ are principals in Niadyne Inc., whose sponsored research is managed in accordance with the University of Arizona conflict-of-interest policies. Dr Draelos owns no stock in Niadyne and has no other financial interest in the corporation.

## References

1 Li M, Marubayashi A, Nakaya Y, Fukui K, Arase S. Minoxidil-induced hair growth is mediated by adenosine in cultured dermal papilla cells: possible involvement of sulfonylurea receptor 2B as a target of minoxidil. *J Invest Dermatol* 2001; **117**: 1594–600.

2 Jacobson EL, Giacomoni PU, Roberts MJ, Wondrak GT, Jacobson MK. Optimizing the energy status of skin cells during solar radiation. *J Photochem Photobiol B* 2001; **63**: 141–7.

3 Jacobson MK, Jacobson EL. Discovering new ADP-ribose polymer cycles: protecting the genome and more. *Trends Biochem Sci* 1999; **24**: 415–7.

4 Lee HC. Multiplicity of $Ca^{2+}$ messengers and $Ca^{2+}$ stores: a perspective from cyclic ADP-ribose and NAADP. *Curr Mol Med* 2004; **4**: 227–37.

5 Kim H, Jacobson MK, Kim M, Jacobson EL, Qasem J. A topical niacin prodrug enhances wound healing by stimulation of leptin secretion. *J Invest Dermatol* 2002; **119**: 347.

6 Komuves LG, Hanley K, Man MQ, Elias PM, Williams ML, Feingold KR. Keratinocyte differentiation in hyperproliferative epidermis: topical application of PPAR alpha activators restores tissue homeostasis. *J Invest Dermatol* 2000; **115**: 361–7.

7 Sano S, Itami S, Takeda K, *et al.* Keratinocyte-specific ablation of Stat3 exhibits impaired skin remodeling, but does not affect skin morphogenesis. *Embo J* 1999; **18**: 4657–68.

8 Tunaru S, Kero J, Schaub A, *et al.* PUMA-G and HM74 are receptors for nicotinic acid and mediate its anti-lipolytic effect. *Nat Med* 2003; **9**: 352–5.

9 Jacobson MK, Tashtoush B, Coyle DL, *et al.* Elevation of skin cell NAD content by topical application of pro-nad compounds. *J Invest Dermatol* 2000; **114**: 849.

10 Jacobson EL, Kim H, Kim M, Wondrak GT, Jacobson MK. Developing topical prodrugs for skin cancer prevention. In: DS Alberts, LS Hess, eds. *Fundamentals of Cancer Prevention*. Berlin, Heidelberg, New York: Springer; 2005: pp. 139–60.

11 Ludwig E. Classification of the types of androgenetic alopecia (common baldness) occurring in the female sex. *Br J Dermatol* 1977; **97**: 247–54.