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CONCISE COMMUNICATION

Melatonin increases anagen hair rate in women with androgenetic alopecia or diffuse alopecia: results of a pilot randomized controlled trial

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Summary

Background In addition to the well-known hormonal influences of testosterone and dihydrotestosterone on the hair cycle, melatonin has been reported to have a beneficial effect on hair growth in animals. The effect of melatonin on hair growth in humans has not been investigated so far.

Objectives To examine whether topically applied melatonin influences anagen and telogen hair rate in women with androgenetic or diffuse hair loss.

Methods A double-blind, randomized, placebo-controlled study was conducted in 40 women suffering from diffuse alopecia or androgenetic alopecia. A 0·1% melatonin or a placebo solution was applied on the scalp once daily for 6 months and trichograms were performed to assess anagen and telogen hair rate. To monitor effects of treatment on physiological melatonin levels, blood samples were taken over the whole study period.

Results Melatonin led to a significantly increased anagen hair rate in occipital hair in women with androgenetic hair loss compared with placebo ($n = 12$; $P = 0{\cdot}012$). For frontal hair, melatonin gave a significant increase in the group with diffuse alopecia ($n = 28$; $P = 0{\cdot}046$). The occipital hair samples of patients with diffuse alopecia and the frontal hair counts of those with androgenetic alopecia also showed an increase of anagen hair, but differences were not significant. Plasma melatonin levels increased under treatment with melatonin, but did not exceed the physiological night peak.

Conclusions To the authors' knowledge, this pilot study is the first to show that topically applied melatonin might influence hair growth in humans *in vivo*. The mode of action is not known, but the effect might result from an induction of anagen phase.

Key words: anagen hair, androgenetic alopecia, diffuse alopecia, melatonin, randomized controlled trial

As well as effects on regulation of human hair growth caused by sex hormones such as testosterone or dihydrotestosterone,[1] there is evidence for the involvement of other hormones in the human hair cycle.[2] Until now, melatonin has not been investigated in humans, but some studies report positive effects of melatonin in animals. The mitotic activity of hair matrix cells normally increases during the winter and decreases in the spring. After loss of coat hair, melatonin is responsible for induction of a new hair cycle. Cashmere goats showed an acceleration of hair cycle induction under the influence of melatonin[3] and New Zealand goats receiving melatonin had an induced anagen phase after springtime hair loss of telogen follicles.[4] *In vitro* studies with cashmere goat follicles also showed a positive effect of melatonin on hair matrix cell proliferation and hair growth.[5] We performed a clinical study to investigate the effect of topically applied melatonin on hair growth in women.

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Materials and methods

Patients and treatment

A double-blind, randomized, placebo-controlled study was conducted in 40 women aged 20–70 years. Subjects had been clinically diagnosed as having diffuse alopecia (28 women) or androgenetic alopecia (12 women) and entered the study after giving informed consent. The diagnosis of androgenetic alopecia was made clinically according to the scoring of Ludwig,[6] when the patient showed a decrease in hair density over the top of the head with a more or less marked stripe with relatively dense hair in the forehead hair border and the occipital region. Diffuse alopecia was diagnosed clinically when diffuse thinning of the hair was seen all over the scalp. Thyroid disease or iron deficiency were excluded by thyroid hormone tests and ferritin and serum iron levels.

This study has been approved by the Jena University Ethics Committee.

The participants applied a 0·1% melatonin–alcohol solution (melatonin, high-purified; Helsinn Chemicals, Biasca, Switzerland) or alcohol solution alone topically once daily in the evening for 6 months. The daily amount to be applied was 1 mL given in eight spray hits ($8 \times 0{\cdot}128$ mL $= 1{\cdot}024$ mL).

Methods

Trichograms were taken in defined areas in the frontal and occipital regions of scalp hair before treatment and after 3 and 6 months of treatment. They were taken as follows: the volunteers were instructed not to wash their hair for the 5 days before the trichogram. For the frontal trichogram a point 2 cm left or right of the median line of the scalp and 2 cm behind the frontal hair line was chosen and hair was combed longitudinally. The occipital trichograms were taken at a point 2 cm left or right of the protuberantia occipitalis. In each case, about 50–80 hairs were fixed with a rubber armed clip and pulled out strongly to obtain the entire hairs with their roots. They were put on a specimen slide and fixed with transparent tape. The anagen, catagen and telogen hairs were counted using a microscope (× 20 magnification) and their percentages calculated.

To assess the influence on plasma melatonin levels during treatment, blood samples were taken weekly in the first 2 months and then monthly until the end of the study. Melatonin was extracted from human blood by vacuum extraction combined with centrifugation in a multistep procedure using methanol, distilled water and hexane. Then melatonin was measured by a specific melatonin double antibody radio immunoassay (Melatonin-RIA; DPC Biermann, Bühlmann Laboratories AG, Bad Nauheim, Germany) using a radiolabelled melatonin tracer (^{125}I-melatonin) and a melatonin antibody (Kennaway G280; Billmann Laboratories AG, Bad Nauheim, Germany). During a 20-h incubation period ^{125}I-melatonin competes with melatonin from the sample for the antibody. A second antibody marks the ^{125}I-melatonin–antibody complexes and radioactivity is measured in a gamma counter. The ^{125}I-melatonin concentration is inversely proportional to the melatonin concentration in the blood sample.

Statistics

Mean and SD trichogram values were calculated separately for the melatonin and placebo groups by means of Microsoft Excel software. To evaluate the effect of melatonin treatment compared with placebo treatment after 6 months a generalized estimation equation (GEE) of the anagen and nonanagen (telogen) hair counts was used, with a binomial family and patient as clustering parameter.[7] The absolute numbers of hairs counted were used for this analysis. The odds ratio (OR) of anagen hair count to nonanagen hair count was used to quantify average follicle state. The major end-point of the study was a significantly larger OR of hair count after melatonin treatment compared with placebo treatment.

Results

The trichograms showed a more distinct increase of anagen hair rates and decrease of telogen hair rates in melatonin-treated women compared with the placebo group. The anagen hairs in frontal trichograms increased from 80·4% to 82·6% and the telogen hairs decreased from 18·9% to 15·9%. These differences were not statistically significant when looking at the population as a whole. When the population was divided into two groups according to diagnosis the group with androgenetic alopecia ($n = 12$) treated with melatonin showed an increase of anagen hairs in occipital trichograms from 76·3% pretreatment to 85% at the end of the study. In these trichograms the OR of anagen to nonanagen hairs in melatonin-treated women showed a significant effect at 1·90 (95% confidence interval, CI 1·22–2·96; $P = 0{\cdot}012$) compared with the OR in placebo-treated women (Fig. 1).

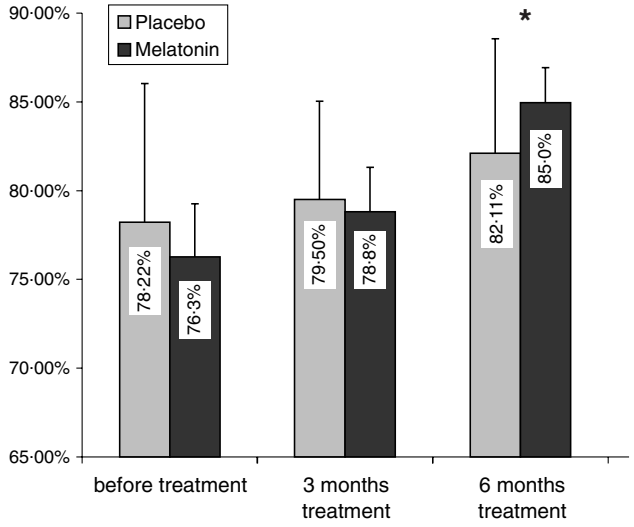

Figure 1. Occipital trichograms of patients with androgenetic alopecia ($n = 12$) show a significant increase in mean ± SD anagen rate after treatment with melatonin compared with placebo (*$P = 0{\cdot}012$).

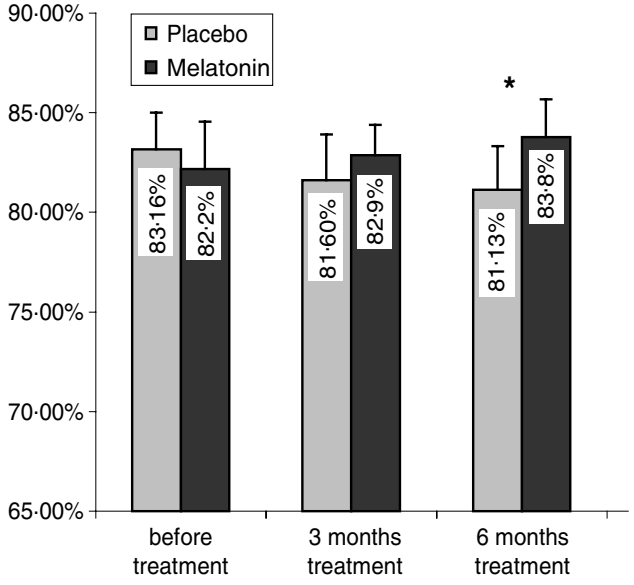

Figure 2. Frontal trichograms of patients with diffuse alopecia ($n = 28$) show a significant increase in mean ± SD anagen rate after treatment with melatonin compared with placebo (*$P = 0{\cdot}046$).

Treatment with melatonin almost doubled the OR in favour of anagen hairs.

In patients with diffuse alopecia ($n = 28$) the frontal hair counts showed a significant effect of the OR of 1·41 (95% CI 1·05–1·90; $P = 0{\cdot}046$). The anagen hair rates in women treated with melatonin increased from 82·2% to 83·8% (Fig. 2).

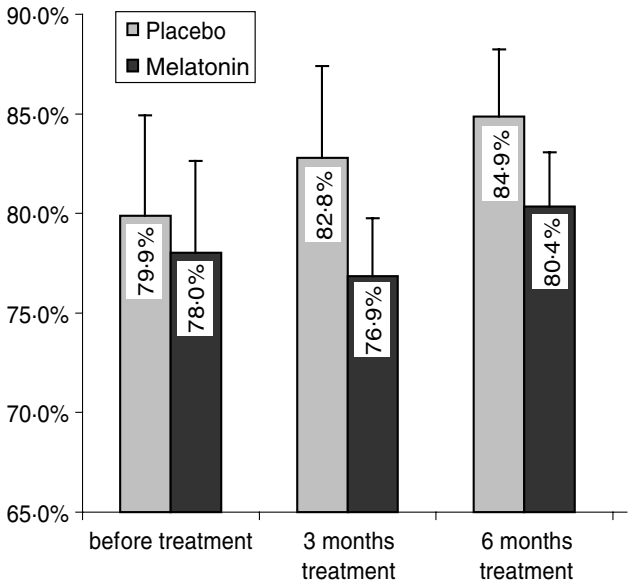

Figure 3. Frontal trichograms of patients with androgenetic alopecia ($n = 12$) show a nonsignificant increase in mean ± SD anagen rate after treatment with placebo and melatonin.

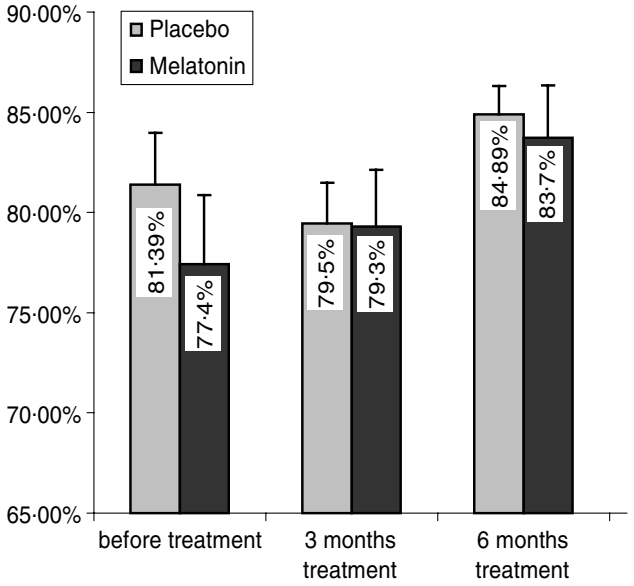

Figure 4. Occipital trichograms of patients with diffuse alopecia ($n = 28$) show a nonsignificant increase in mean ± SD anagen rate after treatment with placebo and melatonin.

No significant effects were found in the frontal hair counts of women with androgenetic alopecia and the occipital hair counts of those with diffuse alopecia (Figs 3 and 4). The results of GEE analysis are shown in Table 1.

Table 1. Generalized estimation equation analysis of the odds ratio (OR) of anagen hair count to nonanagen hair count in frontal and occipital trichograms in androgenetic and diffuse alopecia

Diagnosis		OR	95% confidence interval	*P*-value
Androgenetic alopecia	Frontal	0·91	0·52–1·61	NS
	Occipital	1·90	1·22–2·96	0·012
Diffuse alopecia	Frontal	1·41	1·05–1·90	0·046
	Occipital	0·91	0·58–1·43	NS

NS, not significant.

Melatonin was resorbed by scalp skin and led to plasma levels of between 35 and 50 pg mL^{-1}, which were significantly higher than in the placebo group with constant levels of 5–10 pg mL^{-1}. There was a high inter- and intraindividual variability of melatonin levels in both the melatonin and the placebo group, although melatonin levels in the treatment group did not exceed the physiological night peak of 250 pg mL^{-1}.

Discussion

This is the first study to show an influence of topical melatonin in women with diffuse or androgenetic hair loss. After 6 months treatment there was a larger OR of hair counts in favour of anagen hairs in the melatonin-treated group compared with the placebo-treated group. This was significant for occipital trichograms in androgenetic alopecia and for frontal trichograms in diffuse alopecia.

Interestingly, hair in the frontal region of women with androgenetic alopecia is normally more thinned out than in the occipital region,[6,8] and melatonin failed to increase the anagen hair rate in this area. This might be explained by the fact that the hypersensitivity of hair roots to androgens and the number of androgen receptors in the typically frontoparietal vertex region of female pattern androgenetic alopecia are very high.[9] In contrast to male androgenetic alopecia, this hypersensitivity in women is supposed to be more important than the absolute amount of androgens because the levels of testosterone and dihydrotestosterone are many times lower than in men.[10] The hormonal mode of action in the frontal area of women with androgenetic hair loss can probably not be interrupted by relatively nonspecific substances such as melatonin.

Melatonin led to a significant effect in frontal hair counts of patients with diffuse alopecia. Diffuse alopecia is a symptom-based diagnosis which is not specified exactly; it may be caused by, for example, nutritive factors, toxic agents and low blood perfusion of the scalp skin disturbing the physiological balance of hair growth.[11–13] In this context, melatonin may act as an inducer of hair growth, but only on condition that these factors do not predominate.

It has to be noted that the significant differences in anagen hair density were reached in a total number of 40 test persons, 20 in the melatonin group and 20 in the placebo group. Subsets related to diagnosis were smaller, with 12 in the androgenetic and 28 in the diffuse alopecia group. The study has to be regarded as a pilot study and the preliminary results encourage the authors to repeat the study with a larger number of patients.

Nothing is known about the mechanisms of action of melatonin in human scalp hair. It would be a further aim to investigate this in an *in vitro* model. In accordance with the results from animal models, an analogous mode of action is suggested in humans, i.e. induction of an early anagen phase after the loss of telogen hairs.

Acknowledgments

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