Latest Hair Investigations and Medical Treatments

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Disclosure of Potential Conflicts of Interest

I have performed clinical studies, given lectures, received honoraria, or had consulting activities for the following companies (in order of alphabet):

- Apomedica (Switzerland)
- Asatona (Switzerland)
- Biolab (Brazil)
- Cipla (India)
- Johnson & Johnson
- Lexington
- Merz Pharma (Germany)
- MSD
- Permamed (Switzerland)
- Procter & Gamble
- Rausch (Switzerland)
- Spirig (Switzerland)
- Vichy
- Wolff (Germany)
Latest Investigations in Age-Dependent Loss of Hair
Age-Dependent Hair Loss

Premature aging syndromes with early onset alopecia

Androgenetic alopecia (AGA)
Female pattern hair loss (FPHL)

Senescent alopecia

Progeria

AGA

FPHL

Senescent alopecia

Advancing Age

Puberty 25 y. 35 y. 40 y. 60 y.
Premature Aging Syndromes

Very rare

Of particular interest, since they may reveal **insights into the role of specific molecules for the aging process, growth, and pigmentation of hair**

Premature aging syndromes with **early-onset loss of hair and/or graying**:
- **Hutchinson-Gilford syndrome** (nuclear lamina A)
- **Werner syndrome** (DNA helicase, shorter-than-longer length telomere maintenance)
- **Rothmund Thomson syndrome** (DNA helicase)
- **Laron syndrome** (HGF/IGF-1)

**Analogy with physiologic aging challenged**, and conditions rather viewed as deviations from normal development, specifically impairment of the inductive phenomena of mesenchymal tissue necessary for differentiation and development of different organs

Some classified in the large group of idiopathic dwarfism with **reduced levels of both HGF and IGF-1**
Androgenetic Alopecia

Genetically determined, androgen induced, age-dependent progressive loss of hair with sex-dependent differences in pattern of alopecia


Hamilton-Norwood Scale

Hair growth parameter changes same as in androgenetic alopecia: decrease in hair growth rate, anagen/telogen rate, and hair diameter

Pathogenesis less clear

Probably heterogeneous, and distinction should be made between alopecia with early or late onset and with or without hyperandrogenemia
Androgens
+ Androgen metabolism

Polygenic Trait

Progressive shortening of anagen phase

Reduction of volume of dermal papilla

Hair follicle miniaturization

Increased shedding of hair:
Telogen effluvium

Decreased hair growth:
Terminal-to-vellus hair transformation

Oral Finasteride

Topical Minoxidil

Hair follicle miniaturization

Histopathology

Role of follicular micro-inflammation and fibrosis?

Increased shedding of hair:
Telogen effluvium

Decreased hair growth:
Terminal-to-vellus hair transformation

Trichogram

Trichoscopy
Hair Follicle Microinflammation and Fibrosis

1993 Whiting demonstrates in morphometric studies on patients with male pattern androgenetic alopecia (AGA) a **frequency of 40% significant perifollicular inflammation and fibrosis**, and finds with 55% of patients with follicular inflammation and fibrosis vs. 77% in those without, **lesser regrowth in response to treatment** with minoxidil.

2004 Deloche et al demonstrate in a study of the scalp in a large cohort of volunteers with AGA using macrophotographs presence of **peripilar signs** (PPS) around the hair ostia, and find a significant relationship between PPS and superficial perifollicular infiltrates in early AGA.

2000 Mahé et al propose in a review on AGA and inflammation term „**microinflammation““ in contrast to the inflammatory and destructive process in the classical inflammatory scarring alopecias.
Degeneration of Selected Follicles by Programmed Organ Deletion?

In back skin sections form C57BL/6 mice, perifollicular inflammatory cell clusters (PICC) were found located around the distal non-cycling portion of 2% of hair follicles.

PICC consisted of macrophages (MAC) and CD4+ cells.

During anagen and catagen 10% of PICC+ hair follicles showed degenerative phenomena reminiscent of scarring alopecia.

This may indicate existence of a physiological program of MAC-dependent controlled follicle degeneration by which damaged or malfunctioning follicles are removed.

Scarring alopecia may represent an exaggerated form of this physiological program.

In 2005 Olsen acknowledges existence of clinically significant inflammatory phenomena and fibrosis in androgenetic alopecia and proposes the term „cicatricial pattern hair loss“


Follicular microinflammation and fibrosis:
Whiting D. Diagnostic and predictive value of horizontal sections of scalp biopsy specimens in male pattern androgenetic alopecia.
JAAD 1993;28:755-763

Kossard S. Postmenopausal frontal fibrosing alopecia. Scarring alopecia in a pattern distribution.
Arch Dermatol. 1994;130:770-4

Zinkernagel MS, Trüeb RM. Fibrosing alopecia in a pattern distribution: patterned lichen planopilaris or androgenetic alopecia with a lichenoid tissue reaction pattern?
Arch Dermatol 2000;136:205-11
Revised Concept of Pathobiology and Treatment of Androgenetic Alopecia

1. Genetic factors
   - Polygenic transmission: Polymorphisms of androgen receptor?
   - Others?

2. Precipitating factors
   - Androgens
   - Steroidogenic enzyme activity
   - Others: Microbes, irritants, pollutants, UVR?

3. Follicular microinflammation
   - Radical oxygen species, Nitric oxide
   - Androgen receptor
   - T-cells
   - Macrophages
   - Langerhans cells
   - Mast cells
   - Granulocytes

4. Dermal papilla fibroblasts
   - IGF-1, SCF
   - Others?

5. Follicular epithelium
   - Follicular stem cells
   - Hair matrix keratinocytes
   - Apoptosis
   - Catagen induction

6. Therapeutic strategies:
   1. Gene therapy?
   2. Modifiers of androgen metabolism: finasteride, dutasteride
   3. Antimicrobial treatments?
   4. Antiandrogens: CPA, spironolactone
   5. Hair growth promoters: minoxidil
   6. Antiinflammatory agents?
   7. Apoptosis modulating agents?
   8. Hair transplantation/implantation of dermal papilla cells or cells of follicle dermal-sheath

7. Perifollicular fibrosis?
   - Cytokines, growth factors, chemokines: IL-1, TNFα, TGFβ
   - IL-8, MCP-1, MCP-3
   - Others

8. Stem cell apoptosis?
   - Hair follicle miniaturization
   - Apoptosis

9. Hair follicle loss
   - Permanent hair loss
   - Vellus hair-transformation

Androgens + Androgen metabolism

Polygenic Trait

**Oral Finasteride**

Progressive shortening of anagen phase
Reduction of volume of dermal papilla
Hair follicle miniaturization

**Topical Minoxidil**

Increased shedding of hair:
Telogen effluvium

Decreased hair growth:
Terminal-to-vellus hair transformation

**Antiinflammatory Treatment?**

Histopathology

Increased shedding of hair:
Telogen effluvium

Decreased hair growth:
Terminal-to-vellus hair transformation

Trichogram

Trichoscopy
Fibrosing alopecia in a pattern distribution, F, 69 years old, after 6, 12, and 15 months treatment with oral hydroxychloroquine, and topical 5% minoxidil 0.2% triamcinolone acetonide lotion

(Personal observation)
Hair cycling in a random mosaic pattern

Control of hair cycling within the hair follicle itself

Influence of systemic and external factors:
- hormones
- cytokines
- toxins
- deficiencies (nutrients, vitamins, energy)

Daily telogen shedding: 35-100

Mildred Trotter (1899-1991)

Hair Cycle

Anagen

Katagen

Telogen

Exogen
What’s New in the Hair Cycle?

Hair cycling in a random mosaic pattern
Control of hair cycling within the hair follicle itself
Influence of systemic and external factors
Influence of the local milieu at the level of the follicular stem cells

Hypoxia, HIF1
Pharmacologic target: Stemoxydine® (Propyl-4-hydroxylase inhibitor)
Androgens

Androgen metabolism

Polygenic Trait

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Trichoscopy

Histopathology
Effect of Cigarette Smoke on Hair

There are significant positive associations between premature hair loss and smoking


After 3 months whole-body cigarette smoke exposure, C57BL/6 mice developed areas of alopecia and grey hair. Cell apoptosis occurred massively in the hair bulbs at the edge of alopecia areas.


- effect on microcirculation
- direct (geno-) toxic effect
- imbalance in the follicular protease/antiprotease systems involved in tissue remodelling and the hair follicle cycle
- oxidative stress
- inhibition of aromatase, hydroxylation of E2, relative hypoestrogenic state

Trüeb RM. Association between smoking and hair loss: another opportunity for health education against smoking? Dermatology 2003;206:189-191
Effect of Cigarette Smoke on Hair Growth

In a population study of Asian men smoking status, current amount of cigarette smoking, and smoking intensity were statistically significant factors responsible for AGA after controlling for age and family history. **Patients with early-onset AGA should receive advice early to prevent more advanced progression.**

Su LS, Chen THH. Association of androgenetic alopecia with smoking and ist prevalence among Asian men. Arch Dermatol 2007;143:1401-1406

Premature senescence of balding DPC *in vitro* in association with expression of p16(INK4a)/pRB suggests that **balding DPC are sensitive to environmental stress** and identifies alternative pathways that could lead to **novel therapeutic strategies for treatment of AGA.**


High-dose environmental cigarette smoke induces apoptosis-related alopecia in mice, and **oral administration of L-cystine/vitamin B6 is an effective preventive treatment.**

Androgens

Androgen metabolism

Polygenic Trait

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Oral Finasteride

Oral CYP complex

Topical Minoxidil

Topical Stemoxydine®

Hair follicle miniaturization

Antiinflammatory Treatment?

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Trichoscopy

External Factors

Oral CYP complex
Double-Blinded, Placebo-Controlled Study in Healthy Women with Hair Loss Using Oral Combination of Cystine, Yeast and Pantothenic Acid (CYP)

Active compound led to statistically significant improvement and normalization of mean anagen hair rates within 6 months of treatment, independent of age and presence of female androgenetic alopecia.

From: Lengg et al. Dietary supplement increases anagen hair rate in women with telogen effluvium: results of a double-blind placebo-controlled trial. Therapy 2007;4:59
Metanalysis of Studies Performed with Oral Combination of Cystine, Yeast and Pantothenic Acid (CYP)

Anagen rates – average difference between baseline and close-out
Verum vs. Placebo: 3.83 absolute points improvement in anagen rates (n = 180)

Analysis was carried out using the full analysis set with a fixed-effect model, p-value from test of overall difference between verum and placebo.
Error bars represent standard error of the mean.

From: Finner A. Poster, EHRS 2011 Jerusalem
Biology of Premature Hair Aging

**Intrinsic (Chronologic) Aging:**
- Genetic: AGA, familial premature graysing (AD), progerias (rare)
- Hormones und hormone metabolism: AGA
- Replicative senescence: Graying, senescent alopecia?
- Oxidative metabolism (melanogenesis): Graying

**Extrinsic (Accelerated) Aging:**
- Oxidative stress from tobacco smoking
- Genotoxic effect and oxidative stress from UV-R
- Others (e.g. pollutants)?
# Senescent Alopecia

<table>
<thead>
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<th>Androgenetic alopecia</th>
<th>Senescent alopecia</th>
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<tbody>
<tr>
<td><strong>Onset</strong></td>
<td>Early (teens, twens)</td>
<td>Late (60 years +)</td>
</tr>
<tr>
<td><strong>Distribution</strong></td>
<td>Patterned</td>
<td>Diffuse</td>
</tr>
<tr>
<td><strong>Pathophysiology</strong></td>
<td>Increased activity of 5-α reductase (DHT) in men</td>
<td>Senescence (decreased activity of 5-α reductase )</td>
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<tr>
<td><strong>Genetics</strong></td>
<td>Polygenic</td>
<td>Unknown</td>
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<tr>
<td><strong>Association or risk factor for other diseases</strong></td>
<td>Cardiovascular diseases Benign prostatic hyperplasia Prostate cancer</td>
<td>Age-related disorders?</td>
</tr>
<tr>
<td><strong>Gene expression profiles</strong></td>
<td>Decreased expression of genes required for anagen onset and maintenance / increased expression of catagen and telogen inducers</td>
<td>Increased expression of markers for mitochondrial dysfunction and oxidative stress</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td>Minoxidil Finasteride</td>
<td>Minoxidil Nutritional supplements?</td>
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### Aging and Hair Loss

- **Progeria**
- **Puberty**
- **Advancing Age**
- **AGA**
- **FPHL**
- **Senescent alopecia**

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**Note:** The table and diagram summarize key differences between androgenetic alopecia and senescent alopecia, including onset, distribution, pathophysiology, genetics, association with diseases, gene expression profiles, and potential treatments. The diagram illustrates the progression of hair loss with advancing age and highlights different stages and conditions.
Minoxidil is Effective in Treatment of Female Alopecia at 65+

Senescent alopecia, F, 84 years old, after 3 and 6 months treatment with topical 2% minoxidil lotion

(Personal observation)
Minoxidil is Effective in Treatment of Male Alopecia at 65+

Male androgenetic alopecia, M, 70 years old, after 6 months treatment with topical 5% minoxidil lotion

(Personal observation)
Combination Therapy with Oral CYP Complex

Androgenetic alopecia, M, 61 years old, heavy smoker, after 6 months combination treatment of 1 mg oral finasteride with cystine, medicinal yeast, panthothenic (CYP) complex –based oral supplementation after adding on to preexisting topical minoxidil

(Personal observation)
And How About Low Level-Laser Therapy?

Original evidence that laser and light sources may enhance hair growth:

In 1967, Endre Mester in Semmelweis University in Budapest, Hungary experimented with the effects of lasers on skin cancer. While applying lasers to the backs of shaven mice, he noticed that the shaved hair grew back more quickly on the treated group than the untreated group.


In 1983, Rampen et al report development of hypertrichosis in PUVA-treated patients.


In 2000, Ferrando et al first report of paradoxical hair growth in patients treated with IPL for removal of unwanted hair (photoepilation)

Paradoxical Hair Growth from Treatment (of Hypertrichosis and Hirsutism) with Light and Laser Sources

In fact, the phenomenon of paradoxical hair growth has now been widely acknowledged to occur:

- with an incidence rate ranging from 0.6 to 10 percent
- with low fluences
- all laser types

It is understood to be the result of suboptimal fluences that are too low to induce thermolysis, but high enough to stimulate follicular hair growth.

Hypothesised Mechanism of Action of LLLT

LLLT displaces nitric oxid (NO) from cytochrome c oxidase (COX) allowing an influx of oxygen to bond to COX and progress forward in the respiratory process to ATP synthase and ATP production.

Courtesy of Michael Hamblin, LLLT Mechanisms of Action, ISHRS 2009
Hypothesised Mechanism of Action of LLLT

What happens next?

- ATP synthesis
- Increased mitochondrial respiration
- DNA & RNA Synthesis
- Cell proliferation
- Decreased Apoptosis and Cell Death
- Cell migration
- Differentiation to myofibroblasts
- Collagen synthesis
- Expression of bFGF, VEGF, TGFβ
- Neurotransmitter Synthesis
- Endorphin peptide synthesis
- Changes in catecholamines and biogenic amines (histamine and serotonin)
- Increased blood flow

Courtesy of Michael Hamblin, LLLT Mechanisms of Action, ISHRS 2009
Evaluation of Activity of Laser Doses On Ex-Vivo Hair Growth

Results:
- Laser devices P induced increased hair growth elongation on day 3 of hair fiber measurement
- Laser devices P induced statistically significant ex-vivo increase in hair growth vs. control device after 3 and 7 days

Courtesy of Michael R. Hamblin, PhD, Wellman Center for Photomedicine, Harvard-MIT, Division of Health Sciences & Technology
The Effect of Low-power Laser on the Murine Hair Growth

12 days after laser treatment, many anagen hair follicles on the laser-treated area were found while there were few hair follicles on the non-treated area. (Fig 5, 6)

[ Fig.5 ] Small and black-colored spot (hair follicles) is confirmed to exist in a high density in the dermis.

HairMax LaserComb® Laser Phototherapy Device in the Treatment of Male Androgenetic Alopecia
A Randomized, Double-Blind, Sham Device-Controlled, Multicentre Trial

Matt Leavitt,¹ Glenn Charles,² Eugene Heyman³ and David Michaels⁴

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2 Private Hair Transplantation and Restoration Practice, Boca Raton, Florida, USA
3 Biostatistician, Montgomery Village, Maryland, USA
4 Lexington International, LLC, Boca Raton, Florida, USA
Hypothesised Mechanism of Action: Antiinflammatory Effect

Prior to LLLT therapy, significant inflammation was noticed around the follicles on biopsies that were performed.

Decreased inflammation

Histologic photos courtesy of Dr. Yves Crassas (France).
These photos were part of a study presented at the ISHRS Annual Meeting in Las Vegas, NV in 2007.
Personal Experience with LLLT: Monotherapy
Personal Experience with LLLT: Concomitant Therapy

5% topical minoxidil b.i.d. + LLLT
Concept of Multitargeted Therapy, Integrating LLLT

1 mg oral finasteride daily + 5% topical minoxidil b.i.d. + LLLT

(Personal observation)
Androgens + Androgen metabolism

- Polygenic Trait
- Progressive shortening of anagen phase
- Reduction of volume of dermal papilla
- Hair follicle miniaturization

Increased shedding of hair:
- Telogen effluvium

Decreased hair growth:
- Terminal-to-vellus hair transformation

- Oral Finasteride
- Oral CYP complex
- Topical Minoxidil
- Topical Stemoxydine®
- LLLT

Antiinflammatory Treatment?

Increased shedding of hair:
- Telogen effluvium

- Trichogram

Decreased hair growth:
- Terminal-to-vellus hair transformation

- Trichoscopy

External Factors
- Oral CYP complex
- LLLT
In Summary

While mainstream scientists are working on gene polymorphisms diagnostics for prediction of risk, prevention, diagnosis, and targeted treatment development, on stem cell technologies, and bioengineering of the hair follicle, health care providers are becoming increasingly aware of a more holistic approach to the problem of age-related loss of hair quality and quantity.

Quote: Trüeb RM. Annual P&G Beauty VisionHouse Event at Shangri-La Hotel in Abu Dhabi, United Arab Emirates, December 4 & 5, 2012

Ultimately, combination treatments with topical minoxidil, nutritional supplements, low-level laser therapy, and appropriate scalp care may act synergistic to enhance hair growth. The scientific rationale is given, but there is a need for clinical studies to establish increase in efficacy for combination regimens and adjuvant treatments.

Thank you for your attention!