Medical Treatments for Ageing Male and Female Hairloss and Alopecia

Ralph M. Trüeb, M.D.
Center for Dermatology and Hair Diseases
Bahnhofplatz 1A
8304 Wallisellen (Zurich)
Switzerland

www.derma-haarcenter.ch
Starting Point

„Aged? But he does not appear aged, just look, his hair has remained young“

Marcel Proust (1871-1922), In Search of Lost Time

The appearance of hair plays an important role in people’s overall physical appearance and self-perception.

With today’s increase life-expectation, the desire to look youthful plays a bigger role than ever.

Aging of hair is particularly visible.

The hair care industry has become aware of this and capable to deliver active products directed toward meeting this consumer demand.

The discovery of pharmacological targets and the development of safe and effective drugs also indicate strategies of the drug industry for maintenance of healthy and beautiful hair in the young and old.

Finally, basic scientists interested in the biology of hair growth and pigmentation have exposed the hair follicle as a highly accessible and unique model for the study of age-related effects.
Science of Hair Care and Aging Hair

Esthetic problem of aging hair and its management in terms of
- hair quality
- hair quantity
- hair colour
associated with the aging process

Biological problem of aging hair in terms of
- microscopic
- biochemical
- molecular changes
underlying the aging process
The Hair Aging Phenotype

Hair Weathering and Hair Photoaging

Aging of the Hair Follicle and Hair Pigmentary Unit

- Loss of follicle rigor, consistent with slowing of other body activities with age
- Decrease in rapidity of hair growth
- Reduction in the diameter of the hair shaft
- Failure to pigment the hair shaft (graying)

Aging of Scalp and Age-Related Disorders of Scalp

Age-Related General Problems Affecting the Condition of Hair: nutritional, endocrine, psychological, drug-related, multimorbidity

Age-Dependent Progressive Loss of Hair (Alopecia)

Rare premature aging syndromes with alopecia (Hutchinson-Gilford, Curshmann-Steinert, Rothmund-Thomson, Laron syndrome)

Androgenetic alopecia (male, female)

Senescent alopecia (60 years +)

Farnesylation
Trinucleotide repeats
Helicase HGF/IGF-1

Peculiarities of androgen metabolism
Polygenic trait
External factors

Advancing Age

MAGA
FAGA

Senescent alopecia
Andro(chrono)genetic Alopecia

Genetically determined, androgen induced, age-dependent progressive hair loss with sex-dependent differences in incidence, pattern and severity

<table>
<thead>
<tr>
<th>Age Range</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>18 - 29</td>
<td>12%</td>
<td>3%</td>
</tr>
<tr>
<td>30 - 39</td>
<td>38%</td>
<td>17%</td>
</tr>
<tr>
<td>40 - 49</td>
<td>45%</td>
<td>16%</td>
</tr>
<tr>
<td>50 - 59</td>
<td>52%</td>
<td>23%</td>
</tr>
<tr>
<td>60 - 69</td>
<td>65%</td>
<td>25%</td>
</tr>
<tr>
<td>70 - 79</td>
<td>64%</td>
<td>28%</td>
</tr>
<tr>
<td>&gt; 80</td>
<td>70%</td>
<td>32%</td>
</tr>
</tbody>
</table>

**Hamilton-Norwood I-VII**


**Ludwig I-III**

Androgens +
Androgen metabolism

Genetics

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

Role of follicular microinflammation and perifollicular fibrosis?
Current Treatment for Androgenetic Alopecia

**Kaufman et al.** Long-term treatment with finasteride 1 mg decreases the likelihood of developing further visible hair loss in men with androgenetic alopecia (male pattern hair loss). Eur J Dermatol 2008;18:400-6

Price et al. Changes in hair weight and hair count in men with androgenetic alopecia, after application of 5% and 2% topical minoxidil, placebo, or no treatment. J Am Acad Dermatol 1999;41:717-21
Finasteride in Men Age 40+

24-month, double-blind, randomized, placebo-controlled, multicenter study

424 men 41-60 years with mild-to-moderate, predominantly vertex male pattern hair loss:
- 1mg finasteride: N = 286
- placebo: N = 138

Global photographs of vertex scalp taken at baseline and at months 6, 12, 18, and 24

Patient self-assessments and investigator clinical assessments

Results:

Placebo:
4% improvement
23% worsening

Finasteride:
39% improvement
6% worsening

## Tolerability of Finasteride in Men Age 40+

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Total (%)</th>
<th>Sexual AE’s</th>
<th>Libido</th>
<th>Erection</th>
</tr>
</thead>
<tbody>
<tr>
<td>18-41 Y. (24 M.)</td>
<td>Finasteride 1.6%</td>
<td>Placebo 1.7%</td>
<td>Finasteride 8.1%</td>
<td>Placebo 2.6%</td>
</tr>
<tr>
<td>41-50 Y.</td>
<td>Finasteride 2.6%</td>
<td>Placebo 5.1%</td>
<td>Finasteride 9.4%</td>
<td>Placebo 1.6%</td>
</tr>
<tr>
<td>51-60 Y.</td>
<td>Finasteride 8.2%</td>
<td>Placebo 6.6%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Whiting et al. Efficacy and tolerability of finasteride 1 mg in men aged 41 to 60 years with male pattern hair loss. EurJ Dermatol 2003:13:150-160
Finasteride in Postmenopausal Women

Randomized, double-blind, placebo-controlled study with 1 mg oral finasteride during 12 months in 137 postmenopausal age 41-60 Y.

Study endpoints:
• Hair count
• Global photographic assessment
• Biopsy (morphometric)

Results: For all endpoints no difference in comparison to placebo


5 normoandrogenic postmenopausal women treated with 2.5 – 5 mg oral finasteride for up to 18 months showed improvement on global photographic assessments.

Trüeb et al. Dermatology 2004;209:202-207
Iorizzo et al. Arch Dermatol 2006;142:298-302
Efficacy of Minoxidil in Older Age Group

Prognostic factors for response to topical minoxidil in men:

• Younger age

• Duration of hair loss: < 1 year versus > 10 years

• Duration of balding: < 5 years versus > 21 years

• Diameter of vertex balding: < 5 cm versus > 15 cm

  Rundegren J. (IHRS 2004 abstract B2.4) JDDG 2004;2:500

• Histological presence of significant perifollicular inflammation and fibrosis: Without fibrosis morphometric response to therapy in 77%, with fibrosis in 55%

  Whiting. JAAD 1993;28:755-763
Minoxidil is Effective in Treatment of Alopecia in Women of 60+

Personal observation
Hair Follicle Microinflammation and Fibrosis

1992 Jaworsky et al refer to an inflammatory infiltrate of activated T cells and macrophages in the upper third of the hair follicle associated with an enlargement of the follicular dermal sheath composed of collagen bundles.

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.

2000 Mahé et al propose in a review on AGA and inflammation the term „microinflammation“ in contrast to the inflammatory and destructive process in the classical inflammatory scarring alopecias.

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.
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.

Concept of Cicatricial Pattern Hair Loss

Original report in 1994 by Kossard as a distinct entity in postmenopausal women

Kossard S. Arch Dermatol 1994;130:770-4

In 1997 revised by Kossard et al to be a frontal variant of lichen planopilaris

Kossard et al. JAAD 1997;36:59-66

**Progressive scarring alopecia in a pattern distribution**

with histologic findings of:

• androgenetic alopecia with increased numbers of miniaturized hair follicles with underlying fibrous streamers

• a pattern of follicular interface dermatitis targeting the upper follicle in early lesions

• perifollicular lamellar fibrosis and presence of selectively fibrosed follicular tracts in late lesions

Zinkernagel MS, Trüeb RM. Arch Dermatol 2000;136:205-11
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
Inflammatory Phenomena and Fibrosis

Androgenetic alopecia (diversity of hair shaft diameters)

Androgenetic alopecia with peripilar signs (early)

Fibrosing alopecia in a pattern distribution (late)
Pathobiology of Perifollicular Inflammation and Fibrosis

Inflammation is a **multistep process** with the question arising with regard to the **primary event:**

- Localization of the inflammation near the infundibulum
- **Role of microbial colonization?**
- Specifically, bacterial toxins, antigenic stimulus, and porphyrins?
- **Role of environmental stress from irritants and pollutants?**
- **Role of UVR?**
- Follicular keratinocytes themselves can respond to stressors by producing radical oxygen species, nitric oxid, and **releasing IL-1α**
- Transcription of IL-1 responsive genes: IL-1b, TNFa, IL-8, MCP-1,-3
- **Antigen presentation to T lymphocyte and induction of T-cell proliferation**
- **Sustained inflammation results in connective tissue remodeling (fibrosis),** where collagenases (MMP's) play a role,
- ultimately preventing the follicle to reform a terminal hair follicle in the course of the hair cycle

Role of Cigarette Smoke?

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.

D'Agostini et al. Induction of alopecia in mice exposed to cigarette smoke.. Toxicol Lett. 2000 Apr 3;114(1-3):117-23

- 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
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 is 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 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.

Scalp and hair are altered by both UV-A and UV-B.

A *mottled interfollicular* melanoderma is related to cumulative sun exposures.

There is ample evidence that **AGA ist adversely influenced by UV exposures**


**Actinic field carcinogenesis** of the scalp is responsible for actinic keratoses and SCC of the scalp.

Some specific disorders such as the **red scalp syndrome** are restricted to UVR-exposed scalp.
Revised Concept of Pathobiology and Treatment of Androgenetic Alopecia

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

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

**Follicular microinflammation**
- T-cells
  - Macrophages
  - Langerhans cells
  - Mast cells
  - Granulocytes
- Cytokines, growth factors, chemokines:
  - IL-1, TNFα
  - TGFβ
  - IL-8, MCP-1, MCP-3
  - Others
- Collagenases: Metalloproteinases
- Radical oxygen species, Nitric oxide
- Androgen receptor

**Dermal papilla fibroblasts**
- IGF-1, SCF
- Others?

**Follicular epithelium**
- Follicular stem cells
- Hair matrix keratinocytes
- Apoptosis
- Catagen induction

**Perifollicular fibrosis?**

**Stem cell apoptosis?**

**Hair follicle miniaturization**

**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

Combined Topical Minoxidil And Anti-Inflammatory Treatment

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)
<table>
<thead>
<tr>
<th></th>
<th>Androgenetic alopecia</th>
<th>Senescent alopecia</th>
</tr>
</thead>
<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 (male, female)</td>
<td>Diffuse</td>
</tr>
<tr>
<td><strong>Pathophysiology</strong></td>
<td>Increased activity of $5\alpha$ reductase (DHT)</td>
<td>Senescence (decreased activity of $5\alpha$ reductase)</td>
</tr>
<tr>
<td><strong>Genetics</strong></td>
<td>Polygenic</td>
<td>Unknown</td>
</tr>
</tbody>
</table>
| **Association or risk factor for other diseases** | Cardiovascular diseases
Benign prostatic hyperplasia
Prostate cancer | Age-related disorders? |
| **Gene expression profiles**  | Decreased expression of genes required for anagen onset and maintenance / increased expression of catagen and telogen inducers | Increases expression of markers for mitochondrial dysfunction and oxidative stress |
| **Treatment**                 | Minoxidil
Finasteride
Antiandrogens (controversial)
Estrogens (anecdotal) | Minoxidil
hGH, IGF-1 (anecdotal)
Nutritional supplements? |

Summary: Biology of Hair Aging

Intrinsic (Chronologic) Aging:

- **Genetic:** AGA, familial premature graying (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?
Summary: Hair Anti-Aging

- **Primary prevention:** Hair photoprotection, prevention of tobacco smoking

- **Secondary prevention:** Pharmacologic treatment of AGA with minoxidil and finasteride, and targeting the inflammatory component

- Care of more general, age-related health problems affecting the condition of hair: nutritional deficiency, endocrine disorders, psychological disorders, drug-related, others

- **Role for nutritional supplementations?** Amino acids, vitamins, micronutrients, antioxidants?

- **Role for anti-aging hormonal treatments?** Estrogens, hGH, thyroid replacement therapy, melatonin, others?
Gene polymorphisms diagnostics:
- Prediction of risk
- Prevention
- Diagnosis
- Targeted treatment development
- Personalized medicine (pharmacogenomics)

Stem cell technologies:
- Tissue regeneration


Bioengineering of the hair follicle:
- For reconstructing hair follicles (Phase III studies)

Thank you for your attention!