HABILITATION THESIS

INTRINSIC AND EXTRINSIC SKIN AGING AND POSSIBLE WAYS OF INTERVENTION
Examinations using bioengineering methods

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Field of habilitation: Dermatology & Venerology

The papers listed below in their integrity constitute the topic of habilitation:


The skin, the largest organ of the body, like all other tissues, undergoes degenerative processes during the aging process and is the organ in which changes associated with aging are most visible. Skin aging is associated with increased rates of skin diseases including skin tumors, and with concomitant psychological distress caused by deterioration in appearance. Although the main focus of public medicine is on age-related chronic diseases of other systems such as arthritis, heart disease and cancer, skin aging and diseases related to it have become increasingly important. The average life expectancy has markedly increased over the past decades. A majority of women in developed societies can expect to spend one-third or more of their lifetime in the postmenopausal period, a period with accelerated aging. The external signs of aging are very important for most of them.

Aging is a complex, multi-factorial process caused by chronologic, intrinsic and by exogenous, extrinsic factors. The intrinsic, chronologic type of skin aging comprises genetic disposition, and changes that are due to an oxidative cellular stress and a decrease in cellular functions and that also have an endocrinological background. Extrinsic skin aging is caused by exogenous factors such as UV light, life habits (nutrition, nicotine, alcohol, drugs), catabolic factors (infections, tumors) and other environmental influences.

Intrinsic skin aging is characterized by skin atrophy associated with a loss of elasticity and a decelerated metabolic activity. During the menopause these changes are accelerated, which is why it is during this period of life that many women notice a sudden onset of signs and symptoms of skin aging, such as an increase in skin dryness, loss of firmness, decrease in elasticity and increase in skin looseness. There is a connection between these clinical signs and phenomena such as a decrease in collagen and elastin, changes in basic substance and the ratio of type I to III collagen and alterations in vascularization.

Extrinsic skin aging is mainly influenced by UV irradiation. Photoaging can be seen as the superimposition of effects caused by photodamage on the aging process. These effects include epidermal alterations, e.g. hyperplasia of the horny layer, frequently followed by dysplasia and eventually resulting in neoplastic disorders. Melanocytes and Langerhans’ cells both contribute to the state of epidermal distress and show changes in number and function. Concomitantly, the dermis is also prone to morphological, biochemical and functional changes, a phenomenon that is reflected by the concept of solar elastotic degeneration. A thickening of the skin has
been described during the initial phase of photodamage whereas skin atrophy may eventually develop. In clinical terms, photoaging is characterized by wrinkling, sagging, mottled hyperpigmentation and yellowing. The underlying reason is thought to be the formation of active free radicals and metalloproteinases.

The aim of the papers mentioned here was to examine the effects of both intrinsic and extrinsic factors on skin aging by means of bioengineering methods and to search for possible ways of intervention, with a special focus on the patients’ endocrinological background. My intention was to point out possible effects on skin aging, and to elaborate various methods of intervention in the future.

I.) The first part of my paper deals with intrinsic skin aging, particularly with the endocrinological background of skin aging:


**Measurement of skin thickness by high-frequency ultrasound to objectify the effects of hormone replacement therapy in the perimenopause.** Ultraschall in der Medizin 2001; 22 (5): 219-224.

**Skin aging and sex hormones in women - clinical perspectives for intervention by hormone replacement therapy.** Experimental Dermatology 2004: 13 (Suppl. 4): 36 - 40.

**A prospective, randomized, double-blind, placebo-controlled study on the influence of a hormone replacement therapy on skin aging in postmenopausal women.** Climacteric 2007; 8: in press

The endocrinological influence is one of the main parts of the intrinsic skin aging process. There is mounting evidence that menopause affects some functions of the skin. A hormone replacement therapy (HRT) appears to limit some of the climacteric aspects of cutaneous aging.
The skin is a target organ for various hormones. Sex steroids have a profound influence on both skin development and composition. Hormonal action requires the binding of the hormone to specific receptors. Estrogen and other hormone receptors have been detected, inter alia, in keratinocytes, fibroblasts, sebaceous glands, hair follicles, endocrine glands and blood vessels. Decreased sex hormones thus induce a reduction of those skin functions that are under hormonal control.

That is why we studied skin elasticity, skin surface lipids, skin hydration and skin thickness by non-invasive bioengineering methods in perimenopausal women with and without different kinds of HRT to objectify the endocrinological influence of skin aging.

In all of our above-mentioned studies we showed that skin thickness, which is one of the most relevant parameters in skin aging, increased significantly during HRT (papers 1, 2, 4, 5). Likewise, skin elasticity and skin hydration increased under HRT (papers 1, 4, 5). Skin surface lipids showed no significant changes (paper 5) or increased during combined HRT (papers 1, 4), depending on the type of progesterone, which may reflect the possible stimulatory effects of the progestagen component on sebaceous gland activity whereas estrogen alone had a sebum-suppressive action (paper 1, 4). A comparison of skin hydration and elasticity in UV-exposed and non-exposed areas revealed no significant difference. This finding suggests that both photoaged and UV-protected skin benefit equally from HRT (papers 1, 4, 5). In paper no. 5 we were able to demonstrate that an earlier onset of therapy can produce better results than that a more advanced state of skin aging can only be marginally influenced.

In summary, our results showed improvements in the parameters involved in skin aging with HRT. Without claiming that HRT can or should ever be regarded as an independent treatment for skin aging, we still feel that our findings are interesting as they indicate a beneficial effect of HRT on the skin.
II.) The second part of my papers deals with extrinsic skin aging, especially photoaging:


While there is much information on sunlight-induced photoaging, only few data are available on chronic actinic skin damage due to photochemotherapy (PUVA) treatment. In this study, the effects of PUVA on skin thickness as an aging parameter were compared with the skin thickness of age-matched controls using a high-frequency ultrasound system. The non-lesional skin of psoriasis patients is a useful medium as there is no significant difference compared to the skin thickness of normal people. 124 volunteers (aged 21-88 years, median 52 years, 62 females, 62 males), 62 psoriasis patients who had received PUVA therapy and 62 healthy controls, were investigated. Skin thickness and a subepidermal low-echogenic band (SLEB), a parameter for photodamage, corresponding to actinic elastosis in histology, were measured in 12 different areas.

We found that female skin is thinner than male skin. The skin thickness values of PUVA patients were more markedly decreased than those of the controls for the older patients. There was a clear dependence of the occurrence of SLEB on PUVA therapy in psoriasis patients.

In summary, our study shows that PUVA therapy in psoriasis patients induces changes that may add to the injury by natural sunlight. Moreover, high-frequency ultrasound represents a sensitive non-invasive method for the assessment of skin aging.
Important scientific topics other than the topic of habilitation

I.) Endocrinology - Endocrinologic dermatology

Impact factor: 2.004
The 17β-estradiol/Dydrogesterone combination HRT reduced effectively climacteric symptoms, such as dry skin, loss of hair, increased facial and/or body hair and greasy skin.

Impact factor: 1.832
Our data show that an oral contraceptive containing norgestimate and ethinyl estradiol is a good therapeutic option for women of fertile age suffering from mild to moderate acne vulgaris.

Impact factor: 2.004
By reducing leukocyte adhesion molecule expression on human endothelial cells, an HRT with tibolone may have the intrinsic potential to exert additional, lipid-independent, cardiovascular protective effects that may explain the clinical benefits of cardiovascular diseases in postmenopausal women.

Impact factor: 3.699
Auricular electro-acupuncture significantly reduces pain intensity and analgesic consumption of the opioid remifentanil during oocyte aspiration in IVF treatment.

II.) Further work involving bioengineering


We compared the epidermal hydration and the skin surface lipids of the clinically unaffected skin of patients suffering from atopic dermatitis with that of healthy subjects. Our results show that the dry skin of patients with atopic dermatitis, as previously shown, is due not only to a decrease in skin moisture but also to a reduction of skin lipids. This finding gives rise to a new understanding of the condition, and therefore one should always speak of a hydro-lipid film.


The aim of our study was to compare the immediate and long-term efficacy of low-dose versus medium-dose UVA1 phototherapy for localized scleroderma. Medium-dose UVA1 phototherapy is superior to low-dose UVA1 in the treatment of localized scleroderma. During a follow-up period of one year after cessation of treatment the therapeutic effect is not only sustained but increasing.