TREATMENT OF HAIR THINNING AND HAIR AGEING WITH SPECIFIC LECTICAN AND LEUCINE PROTEOGLYCANS. A REVIEW

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Treatment of Hair Thinning and Hair Ageing with Specific Lectican and Leucine Proteoglycans. A review

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Summary

Research evidence accumulated during the last 20 years on the function and cycling of the hair follicle has demonstrated that certain specific proteoglycans play a central role. Specifically versican and decorin are integral components in this connection.

Various extrinsic and/or intrinsic factors can disturb the delicate balance of specific proteoglycans in the follicle. It is documented that age and stress, among others, can disrupt this balance, and in turn, normal hair follicle function. A decline in structural components, such as several keratins or a shift of apoptotic parameters is often seen in this connection.

Supplementation with bioactive substances can counteract the extrinsic or intrinsic factors and lead to normal hair follicle function. Per-oral OTC supplements containing specific proteoglycans, a fractionated fish extract with specific lectican and leucine proteoglycans**, provide the body and the hair follicles with the crucial and specific bioavailable components needed for normal functioning.

With the results from earlier scientific research on the importance of specific versican and decorin, combined with results from clinical studies using marine extract*** demonstrating significant reduction of hair loss and improvement in re-growth, important deductions can be made.

There is a well-founded scientific basis for recommending proteoglycan replacement therapy as baseline treatment* with subjects suffering from hair loss problems and/or hair growth disorders, as it has been shown that proteoglycan levels decline within the hair follicle both with age and whilst experiencing stress.

In conclusion, supplementation containing marine extract*** can revitalise dysfunctional follicles and open a new era on nutritional factors influencing hair loss and/or hair growth.

In addition to the positive effect on hair growth, it is hypothesised that there may be a positive effect with the use of supplementation containing marine extract*** on hair greying. Theoretically, this is possible, and clinical work we have conducted supports this theory.

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Riassunto

Evidenze sperimentali degli ultimi 20 anni eseguite sul controllo del ciclo di vita dei capelli, hanno posto in evidenza come alcuni proteoglicani, primi fra tutti versican e decorin, giocino un ruolo centrale su tale ciclo. Diversi fattori, quali l'età e lo stress, possono alterare l'equilibrio del ciclo dei capelli, legato anche alle modifiche strutturali delle cheratine o alla vita stessa delle cellule. L'integrazione con sostanze bioattive potrebbero interagire con sia con fattori estrinseci che intrinseci, compensando eventuali equilibri. A tal riguardo l'integrazione orale con particolari proteoglicani contenuti in un estratto di pesce ricco di lectican e leucina, sembra essere utile per arricchire il follicolo pilifero di specifici componenti necessari alla funzione del suo ciclo. Dai risultati ottenuti con precedenti studi che hanno evidenziato l'importanza clinica dei proteoglicani versican e decorin, e dall'efficacia clinica evidenziata dall'uso di particolari estratti marini, sembra possibile dedurre come questi particolari composti possano essere utili ad ottimizzare la ricrescita dei capelli. Vi sono perciò fondate ragioni scientifiche per ritenere come la terapia a base di proteoglicani possa risultare utile per pazienti soggetti ad anomala perdita di capelli o comunque affetti da problemi che ne rallentano la ricrescita, a causa dell'età o di frequenti stress.

In conclusione, l'integrazione alimentare con prodotti contenenti specifici estratti marini, sembra poter essere utile per riequilibrare disfunzioni legate alla vita del follicolo pilifero aprendo nuove strade per curare la ricrescita dei capelli. Inoltre, sembrerebbe anche possibile che l'uso di questi integratori possa modulare anche l'ingrignimento. Il nostro gruppo di lavoro sta conducendo nuovi studi per supportare questa ipotesi.
INTRODUCTION

For the majority of people, the appearance of hair plays an important role in overall physical appearance, confidence, and self-perception, and in modern society the desire to look youthful plays a larger role than ever. The hair care industry is acutely aware of this and so has become more capable of delivering active products that are directed toward meeting this consumer demand (1-4).

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.

Hair ageing is characterised by weathering of the hair shaft and ageing of the hair follicles. Hair follicle ageing presents as a manifestation of a decrease in melanocyte function resulting in hair greying, as well as a decrease in hair production in the form of Androgenetic and Senescent Alopecia. The scalp is also subject to intrinsic or physiological ageing and extrinsic ageing caused by external factors. Intrinsic factors are related to individual genetic and epigenetic mechanisms with individual variations, with common phenotypes including premature greying and Androgenetic Alopecia. Extrinsic factors include ultraviolet radiation and smoking, among others, and experimental evidence supports the hypothesis that oxidative stress plays a role in skin and hair ageing as well.

Topical anti-ageing compounds for hair include humectants, hair conditioners, photoprotectors, and antioxidants. Current available treatment modalities with proven efficacy for treatment of hair loss are topical minoxidil (5), oral finasteride (6), cyproterone acetate (7, 8), spironolactone (9), progesterone (10), autologous hair transplantation (11), laser light therapy (12, 13), and a few natural products (1, 2, 24). In the absence of other ways to reverse hair greying, hair colourants are the mainstay of recovering lost hair colour. Topical liposome targeting for melanins, genes, and proteins selectively to hair follicles are under current investigation (14, 15).

A hair growth cycle treatment product has been developed** by Pharma Medico Group. The main ingredient is an exclusive extract of marine origin*** and is a proprietary fractionated fish extract, containing specific lectican and leucine proteoglycans, specific glycosaminoglycans, proteins, and minerals with small amounts of carbohydrates and lipids. In addition the product contains vitamins and minerals.

The product is available as an OTC food supplement for treatment of hair loss problems and/or hair growth disorders, and is the leading product in this category of the market in, among others, the United Kingdom.

Crude marine extracts, since the early 1990s, have been used in some food supplements for treatment of ageing skin as well as for the treatment of arthritis; in both cases with some success. The medical community is still skeptical of the clinical effects of crude marine extracts, especially in the arthritis field, yet a large number of patients are using marine extract-based preparations in combination with conventional drug therapies with positive results (16-22).

In the treatment of ageing hair, beginning with hair loss, several well-designed studies have been carried out with food supplements in which marine extracts are the main ingredients. Two studies have been carried out as CRT (Controlled Randomised Trials) (23-24) of which one used the proprietary fractionated fish extract with specific lectican and leucine proteoglycans*** (24), as well as another study carried out with open methodology (25). Furthermore, an in-clinic,
medically monitored study was carried out with the product\textsuperscript{a} (1). The experiences from most of these studies are impressive, and show a significant and positive effect on hair growth. Daily dosing also demonstrated that tolerability has been excellent.

In the two CRT studies, the main bulk of the participants were men with Androgenetic Alopecia, also referred to as Male Pattern Hair Loss (MPHL) or common baldness. However, in the in-clinic medically monitored study, a complete female population was used, leading to no gender difference in the efficacy of the fractionated fish extract with specific lectican and leucine proteoglycans reported. In some of the open studies, a female population was also included and no gender differences in the efficacy of the marine extracts were reported. No CRT designed studies have been carried out in relation to Androgenetic Alopecia in females, also known as Female Pattern Hair Loss (FPHL).

**HAIR LOSS IN MALES AND FEMALES**

Androgenetic Alopecia (AGA) affects at least 50\% of men by the age of 50, and up to 70\% of all males later in life (26). Estimates of its prevalence in women have varied widely, though recent studies claim that at least 16\% of women aged less than 50 years are affected, increasing to a proportion of 30-40\% of women aged 70 years and over (27).

The hair loss is heritable, androgen dependent, and occurs in a defined pattern. It is assumed that the genetically predisposed hair follicles are the target for androgen-stimulated hair follicle miniaturisation, leading to gradual replacement of large, pigmented hairs (terminal hairs) by barely visible depigmented hairs (vellus hairs) in affected areas (28). The result is a progressive decline in visible scalp hair density. Whilst male pattern AGA is characterised by the typical bitemporal recession of hair and a balding vertex (26), FPHL is set apart by the diffuse thinning of the crown and intact frontal hairline (29).

While the genetic involvement is pronounced, but poorly understood, major advances have been achieved in understanding principal elements of the androgen metabolism involved in the pathogenesis of AGA (30). Androgen-dependent processes are predominantly due to the binding of dihydrotestosterone (DHT) to the androgen receptor (AR). Dihydrotestosterone-dependent cell functions depend on the availability of weak androgens, their conversion to more potent androgens via the action of 5α-reductase, low enzymatic activity of androgen inactivating enzymes, and functionally active AR present in high numbers. The predisposed scalp exhibits high levels of DHT, and increased expression of the AR. Conversion of testosterone to DHT within the dermal papilla plays a central role, while androgen-regulated factors deriving from dermal papilla cells are believed to influence growth of other components of the hair follicle. Since many extrinsic hair growth-modulatory factors, such as androgens (31), apparently operate, at least in part, via the dermal papilla, research is currently also focused on identifying androgen-regulated factors deriving from dermal papilla cells. Of the several factors that have been suggested to play a role in hair growth, so far only insulin-like growth factor (IGF-1) has been reported as altered in-vitro by androgens (32). Stem cell factor (SCF) has been found to be produced in higher amounts by androgen-dependent beard cells than in control non-balding scalp cells, presumably also in response to androgens (33). Since SCF is the ligand for the
cell surface receptor c-kit on melanocytes, this may also play a role for hair pigmentation.
Finally, the relationship of FPHL to (male pattern) AGA has been challenged. Arguments against FPHL representing the female counterpart of male AGA are: a probable mother-to-daughter transmission of FPHL, a significantly lower incidence of FPHL in women than AGA in men (27), occurrence of FPHL in the absence of circulating androgens (34), lack of response to antiandrogen therapy in normoandrogenetic premenopausal women (35), lack of response to 1 mg oral finasteride daily in postmenopausal women (36), and occurrence of male pattern AGA in women with pathologically elevated androgen levels. It has been suggested that the different pattern of hair loss in the majority of women from that usually seen in men may be due to differences in the relative levels of 5α-reductase, aromatase, and androgen receptors in scalp hair follicles in women compared with those in men (37).

PROTEOGLYCANS AND THE HAIR FOLLICLE

To guarantee the growth of strong and healthy hair, various specialised cell types in the follicle interact in a complex set of molecular signals. Biological alterations due to intrinsic and extrinsic stimuli can destabilise this well-balanced hair growth metabolism (15).
In addition, ageing and lack of oxygen and nutrients could also be characterised as a disturbance in this perfectly organised system, slowly leading to follicle miniaturisation and death. During the period 1991 to 2008 a number of basic research studies have been published showing the presence and importance of proteoglycans (PGs) and glycosaminoglycans (GAGs) on the cycling and proper functioning of the human hair follicle (38-44).
A proteoglycan is comprised of a core protein which has one or more covalently attached glycosaminoglycan (GAG) side chains. GAGs are long, unbranched polysaccharides containing a repeating disaccharide unit (45). One of the biologically active proteoglycans in the proprietary fractionated fish extract *** is a versican.
Versican, a chondroitin sulphate proteoglycan, is one of the main components of the extracellular matrix, which provides a loose and hydrated matrix during key events in development and disease. Versican has an apparent molecular mass of more than 1000kDa, and in 1989, Zimmermann and Ruoslahti cloned and sequenced the core protein of fibroblast chondroitin sulphate proteoglycan. It was designated ‘versican’ in relation to its versatile modular structure. Versican belongs to the lecticin protein family, and is also known as chondroitin sulphate proteoglycan core protein 2 or chondroitin sulphate proteoglycan 2 (CSPG2), and PG-M (50).
Versican participates in cell adhesion, proliferation, migration, and angiogenesis, and hence plays a central role in tissue morphogenesis and maintenance. In addition, versican contributes to the development of a number of pathologic processes including atherosclerotic vascular diseases, cancer, tendon remodeling, hair follicle cycling, central nervous system injury, and neurite outgrowth (50). Versican is a complex molecule consisting of modular core protein domains and glycosaminoglycan side chains, and there are various steps of synthesis and processes regulating them. Also, there are differential, temporal, and spatial expressions of versican by multiple cell types and in different developmental and pathological time frames. To fully appreciate the functional roles of versican as it relates

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to changing patterns of expression in development and disease beyond hair follicle cycling, and thereby the scope of this review paper, an in-depth knowledge of versican’s biosynthetic processing is necessary (46, 47).

Decorin is a prototypical member of the small leucine-rich proteoglycan gene family, which consists of a glycosaminoglycan and protein core with 12 leucine-rich repeats. Quite recently it has been documented that the small decorin plays a pivotal role in hair biology. The research results suggest that decorin may modulate follicular cycling and morphogenesis and act as an anagen inducer (48, 49). It has previously been shown that the structure of decorin undergoes age-dependent alteration, which may contribute to skin fragility in elderly people (50). The product* contains lectican as well as leucine-rich proteoglycans.

The predominant symptom of hair ageing, greying, is addressed in a plurality of research activities, as age-related changes beyond loss of pigmentation remain obscure. It has been reported that hair follicle density, growth rate, and hair diameter all decline with age, but the molecular events underlying the macroscopic alterations are still poorly understood. It has, however, been shown that concordantly to other biological systems, the hair follicle undergoes an ageing process associated amongst others with a decline in structural proteins such as several keratins, or a shift of apoptotic parameters (14, 15).

In order to get marine extract distributed in the body, one has to be able to demonstrate that it is bioavailable. Volpi has published two clinical studies showing that proteoglycans are absorbed and distributed in the body after oral intake (51, 52).

To guarantee the growth of strong and healthy hair, various specialised cell types in the hair follicle interact according to a complex set of molecular signals. Biological alterations due to intrinsic and extrinsic stimuli can destabilise this well-balanced system, thus affecting hair growth or metabolism. Also, ageing could be characterised as a disturbance in this perfectly organised system (53, 54).

Intake of the specific proteoglycans* is a replacement therapy that will improve the function and cycling of the hair follicle. It has been shown that versican also protects the cells from oxidative stress-induced apoptosis (55). This might have an effect on the oxidative stress taking place in the hair follicle which is mainly due to Hydrogen Peroxide (H2O2). Senile greying of human hair has been subject to intense research since ancient times.

Reactive oxygen has been implicated in hair follicle melanocyte apoptosis and DNA damage. It has been shown by FT-Raman spectroscopy in vivo quite recently that human grey hair/white scalp hair shafts accumulate hydrogen peroxide (H2O2) in millimolar concentrations (56). The data from this research feed the long-voiced, but insufficiently proven, concept of H2O2-induced oxidative damage in the entire human hair follicle, inclusive of the hair shaft, as a key element in senile hair greying, which does not exclusively affect follicle melanocytes. This opens new insight for intervention and reversal of hair greying.

Our recent clinical findings demonstrate that the fractionated fish extract with specific lectican and leucine proteoglycans containing versicans and decorin*** can reduce the effects of hair greying, and lends itself to the inherent antioxidative effect of the versicans described above (51). Furthermore, this antioxidative property may play a secondary role in protecting testosterone’s oxidation to dihydrotestosterone (DHT).

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CONCLUSION

In conclusion, supplements containing specific bioavailable proteoglycans* can revitalise dysfunctional hair follicles and open a new era on nutritional factors that influence hair loss. As such, it is beneficial using the product* as a continuous, baseline treatment in all types of hair loss, also when targeting age and stress related hair loss cases, both as a prophylactic (preventative measure), and a therapy (treatment).

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