

# Stress and the Hair Growth Cycle: Cortisol-Induced Hair Growth Disruption

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## ABSTRACT

The stress hormone, cortisol, is known to affect the function and cyclic regulation of the hair follicle.

When cortisol is present at high levels it has been demonstrated to reduce the synthesis and accelerate the degradation of important skin elements, namely hyaluronan and proteoglycans by approximately 40%.

The following discussion outlines the relationship between stress, cortisol, and the effect on the normal function of the hair follicle. As a result of this connection, important correlations have been established in the literature to form a basis for novel, effective treatments of stress-related hair growth disorders.

Amongst various treatment methods and substances, oral supplementation with a specific bioavailable proteoglycan stands out as a promising new therapeutic treatment method.

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## INTRODUCTION

**B**iological organisms are continuously exposed to a myriad of internal and external stimuli and stressors. As a response to these stimuli, living organisms have developed natural defence and adaptation mechanisms over time.

Stress is a common stimulus and well-known causal factor of hair growth disorders and hair loss. The link between psycho-emotional stress and hair loss can be distinguished according to three levels of interaction.<sup>1</sup>

### *Interaction Level 1: Acute or Chronic Stress as a Primary Inducer of Telogen Effluvium*

Telogen effluvium is one of the major hair growth disorders and is closely related to stress. Occurring mainly in women, telogen effluvium can be induced as a result of stress or extreme hormonal imbalance. This creates a disruption to the normal hair growth cycle in which anagen (growing) hairs prematurely enter the telogen (resting) phase. Consequently, symptoms begin to appear in the form of short, sudden bouts of hair shedding with little to no hair growth.<sup>2</sup>

### *Interaction Level 2: Acute or Chronic Stress as an Aggravating Factor in Hair Loss Disorders Whose Primary Pathogenesis is of Endocrine, Toxic, Metabolic, or Immunological Nature (eg, androgenetic alopecia, alopecia areata)*

Androgenetic alopecia is the most common hair growth disorder in women and men. The large majority of hair growth disorders occur due to a change in the hair growth cycle, which is usually androgen dependent and genetically determined. In the case of androgenetic alopecia, testosterone is converted to dihydrotestosterone (DHT) via 5 $\alpha$ -reductase. DHT then binds

to androgen receptors in the hair follicle, which results in the shortening of the anagen phase and simultaneous prolongation of the telogen phase, combined with hair follicle miniaturisation. Symptoms of hair thinning and loss result from a gradual reduction in hair diameter and a visibly widened hair parting.<sup>3,4</sup>

Alopecia areata is an autoimmune disorder that affects men and women equally. It is thought that the development of alopecia areata may occur as a result of an environmental influence on the immune and hormonal microenvironments of the hair follicle. Representing approximately 0.7% to 3.8% of all patients attending dermatology clinics, alopecia areata is characterised by delimited patches of hair loss on the scalp. Hair loss symptoms in this connection can become more widespread, with complete loss of hair on the scalp; alopecia totalis, or by a complete loss of all hair on the scalp and body; alopecia universalis. Moreover, people with alopecia areata may experience a reduced expression of glucocorticoids due to weak response to acute physiological stressors.<sup>5,6</sup>

### *Interaction Level 3: Stress as a Secondary Problem in Response to Prior Hair Loss*

Stress resulting as a consequence of hair loss, in contrast to being a primary inducer or aggravating factor, can lead to further perpetuation of hair loss. This may be due to a vicious cause-and-effect circle arising between stress-as-response and hair fall.<sup>7</sup>

## Stress and the Hair Follicle

The role and function of the hair follicle is sophisticated. Through the continuous, cyclic production of hair fibres, the follicle serves as a sensory organ as well as an instrument of psychosocial communication and protection in humans. This is

done as the hair follicle functions according to an independent growth mechanism called the Hair Growth Cycle. This all important Hair Growth Cycle is comprised of three phases; rapid growth (Anagen), apoptosis driven regression (Catagen), and relative inactivity or rest (Telogen).<sup>3</sup>

After a period of acute or chronic stress many individuals will experience an increased amount of hair loss. In murine studies, chronic stress was significantly associated with hair growth inhibition, increased granulation of mast cells and perifollicular inflammation.<sup>8</sup> Further studies, both in vitro and in vivo, have demonstrated that certain stress-mediating substances such as substance P, adrenocorticotrophic hormone, prolactin, and cortisol actually inhibit the growth of hair.<sup>9-11</sup>

Neural signals have also been demonstrated to modulate hair growth, however this is not essential for the normal function of the hair growth cycle. Moreover, researchers have shown the ability of corticotropin-releasing hormone to directly stimulate isolated hair follicles in humans, with cortisol synthesis and neuroendocrine feedback loops.<sup>1</sup>

Of particular interest are the steroid hormones cortisone and cortisol, which are released in response to stress. As the research cited above posits the direct effect of cortisol on the hair follicle, a direct correlation between cortisol and the development of hair loss can also be identified.

### Cortisol and Cortisol Inhibitors

Studies have indicated a range of side effects on the skin and its structural components resulting from the presence of excess cortisol.<sup>12</sup> In fact, the presence of elevated levels of cortisol has been demonstrated in both males and females with androgenetic alopecia, compared to controls.<sup>13,14</sup>

Measuring the precise effect of cortisol on human connection tissue is not a simple and straightforward task. 'Hair analysis', however, is a common method used to measure the presence of external compounds in the body, especially in relation to illicit or harmful chemical substances.<sup>15</sup> Hair analysis is widely used since the presence of substances in the hair can be tracked over time, due to the fact that hair grows at a steady rate of approximately 1 cm per month.<sup>16</sup> Similarly, this methodology is being applied to measure chronic stress in the body by tracking and quantifying cortisol levels as a biological marker in hair.<sup>17</sup>

When analysing cortisol measurements in the body, interestingly, low cortisol levels have been shown to exert positive effects. Low levels of cortisol actually stimulate, as well as slow the breakdown of hyaluronan and proteoglycans by approximately 25%. However when cortisol is present at high levels the opposite is true, as it has been shown to reduce the synthesis and accelerate the breakdown of these structural skin components (hyaluronan and

proteoglycans) by approximately 40%.<sup>18</sup> As proteoglycans and hyaluronan serve the function of attracting and retaining moisture in the skin, the degradation and reduction of these skin components would present as excessively dry skin.<sup>12</sup>

One known cortisol inhibitor is ketoconazole, an imidazole antifungal agent used to treat dandruff and seborrheic dermatitis. The functionality of ketoconazole has been indicated in vivo, and consequently confirmed in vitro, to inhibit the secretion of cortisol. This is done by blocking 11 beta-hydroxylase activity which is then compensated by high levels of adrenocorticotrophic hormone in vivo.<sup>19</sup>

Researchers have studied the effect of using a 2% ketoconazole shampoo long-term, and it was demonstrated that the size and proportion of hair follicles in the anagen phase, as well as hair density, were improved in the case of androgenetic alopecia. The 2% ketoconazole shampoo was also shown to have an additive effect for androgenetic alopecia when used in combination with finasteride.<sup>20</sup> The positive effect of this 2% ketoconazole shampoo was later confirmed in a small, open study in which it was concluded that ketoconazole may exert its positive effects on androgenetic alopecia in both an androgen-dependent, as well as androgen-independent manner.<sup>21</sup>

### Proteoglycans and Cortisol

For the hair follicle to function properly according to a normal cycle, specialised cells in the follicle must interact according to intricate signalling mechanisms. A number of research studies conducted between 1991 and 2008 demonstrated that the presence of proteoglycans and glycosaminoglycans play an important role on the normal function and cycling mechanism of the hair follicle.<sup>22-28</sup>

Proteoglycans are heavily glycosylated proteins that consist of a core protein, together with one or more covalently attached glycosaminoglycan side chains. Glycosaminoglycans are long, unbranched polysaccharides containing a repeating disaccharide unit.<sup>29</sup>

Specifically, versican is a type of large proteoglycan belonging to the lectican family, and is known as a chondroitin sulfate proteoglycan. Versicans are present in a range of human tissues and comprise one of the main components of the extracellular matrix. This is to provide a loose and hydrated matrix during key events in development and disease. Versicans are known for their role in cell adhesion and are centrally involved in tissue morphogenesis and maintenance. In addition, versicans contribute to the development of a number of pathologic processes including hair follicle cycling.<sup>30</sup>

Decorin is a proteoglycan from the small leucine-rich proteoglycan gene family, and consists of a protein core with

12 leucine-rich repeats and a glycosaminoglycan chain. Decorin is documented to play a pivotal role in hair biology, as studies suggest its ability to modulate cycling and morphogenesis of the hair follicle, as well as acting as an anagen inducer.<sup>31,32</sup>

Although the hair follicle normally functions as a well-balanced biological system, it can become destabilised due to a range of internal and external factors and stimuli.<sup>33</sup> Specifically, high concentrations of cortisol in the body are known to have a damaging effect on proteoglycans in and around the hair follicle.<sup>10,18</sup>

### Treating Stress-Related Hair Loss

Of late, new pharmacological solutions are becoming increasingly recognised as serious treatments for stress-related disorders in the body.

When available, certain corticotropin-releasing hormone receptor antagonists could provide a treatment solution to skin conditions induced or aggravated by stress. However, inhibiting the activation of mast cells is considered a more promising approach in the literature. In this connection only a few clinically available molecules are known to be effective, although recent studies have shown that some flavonols, specifically quercetin, can inhibit both newly synthesised and pre-stored mediators from mast cells in humans.<sup>34</sup> One study has already demonstrated synergistic efficacy between such flavonoids and chondroitin sulphate proteoglycans to inhibit both the activation and secretion of mast cells.<sup>26</sup>

It is further argued in the literature that to treat stress-triggered telogen effluvium, for example, effective pharmacological treatment should entail prolonging the anagen phase of the hair growth cycle.<sup>34</sup> Anagen phase prolongation would help prevent the onset of early catagen, which is crucial, as this is the central mechanism of the telogen effluvium condition.

To achieve this effect, a number of approaches exist which range from the traditional to the more alternative. Popular, traditional treatments for hair loss such as applying minoxidil to the scalp, can achieve anagen prolongation via the opening of potassium channels.<sup>36</sup>

On the other end of the spectrum, alternative therapies such as 'music listening' have also been shown to significantly reduce chronic stress levels by measuring the presence of cortisol in the hair.<sup>37</sup> Yet as recent research indicates, the presence of certain proteoglycans represent a constant element in a stable, well-functioning hair follicle. Naturally, the relationship between proteoglycans and the hair follicle represents a potential treatment which falls between the traditional and the alternative, and which appears to be both novel and effective.

Producing a viable pharmacological treatment in this connection would require the uptake and distribution of proteoglycans

in the body after oral intake, which has been demonstrated in two studies.<sup>38,39</sup> Thus, the intake of specific proteoglycans as a 'proteoglycan replacement therapy' via oral supplementation is a logical and promising approach to improve the function and cycling of the hair follicle.

Not only has it been shown that versican is able to protect cells from oxidative stress-induced apoptosis, but decorin has also been recognised for its anagen inducing properties.<sup>40</sup> According to a recent publication, it was concluded that supplements containing specific bioavailable proteoglycans to revitalise dysfunctional hair follicles have opened a new era on nutritional factors that influence hair loss. In this connection it was recommended that a specific proteoglycan replacement treatment (Nourkrin<sup>®</sup> with Marilex<sup>®</sup> from Pharma Medico) containing specific lectican, leucine versican, and decorin, is beneficial as a baseline treatment for all hair loss types. This treatment is recommended both as a prophylactic and a therapy, and especially in connection to stress-related hair loss cases.<sup>41,42</sup>

### CONCLUSION

Stress can have a detrimental effect on intricate microbiological systems in the body, and especially in relation to the hair follicle. As a response to internal and external stressors, cortisol is released in the body and can eventually build up to excess levels, and studies have demonstrated the ability of cortisol to degrade integral substances in the skin and extracellular matrix, namely hyaluronan and proteoglycans.

In this way, excess cortisol is therefore able to exert a disruptive effect on the fine-tuned mechanism of the hair follicle, leading to the development of hair growth disorders such as androgenetic alopecia, alopecia areata and telogen effluvium.

These causal relationships have led to a new focus on developing pharmacological treatments for hair growth disorders based on a proteoglycan replacement methodology. A proteoglycan supplementation replacement treatment (Nourkrin<sup>®</sup> with Marilex<sup>®</sup> from Pharma Medico) featuring versican and decorin specifically, can play a pivotal role in the induction and prolongation of the anagen phase of the hair growth cycle. In addition, these lectican and leucine proteoglycans have been demonstrated to protect from stress-induced apoptosis as well as to exert a synergistic effect to inhibit the activation and secretion of mast cells in combination with certain flavonoids.

In fact, a specific proteoglycan replacement therapy<sup>3</sup> has been definitively categorised as opening a new era on nutritional factors that influence the Hair Growth Cycle and hair loss. However going forward people suffering from hair growth disorders will still require complex, comprehensive and careful management beyond pharmacological treatment to alleviate clinical symptoms.

The specific proteoglycan replacement<sup>9</sup> methodology further indicates a strong clinical rationale for supplementation against age-related hair growth disorders, as proteoglycan synthesis is generally reduced as a function of age. Moreover, the effect of topical 2% ketoconazole shampoo should be further researched for its ability to inhibit the effects of excess cortisol in a safe manner.

The treatment approaches described herein do not yet address the concomitant psychological implications that arise as a result of stress-induced hair growth disruption. Several physical stress-reducing activities have been shown to reduce cortisol levels, and quite recently, listening to music has been shown to significantly reduce chronic stress levels, as measured by the presence of cortisol through hair analysis.

It can therefore be concluded that addressing and treating the psychological aspects of stress-induced hair growth disorders justifies an equally interesting and important area for future research.

## DISCLOSURES

The author has received Honoria fees as consultant for Pharma Medico.

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