



## Research Article

# Lifestyle Diseases and the Hair Growth Cycle: A multidisciplinary approach using Nourkrin® with Marilex®, a proteoglycan replacement therapy, for anagen induction and maintenance

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**Submitted:** 21 November 2017

**Approved:** 07 December 2017

**Published:** 08 December 2017

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**Keywords:** Androgenetic Alopecia; Risk factor; Cardiovascular disease; Metabolic syndrome; Diabetes; Proteoglycan replacement therapy



## Abstract

Multiple studies have investigated the relationship between androgenetic alopecia and cardiovascular disease, including studies that have identified elevated rates of cardiovascular disease in patients with vertex hair loss, vertex and frontal hair loss, early onset hair loss and rapidly progressive hair loss. In addition, increased risks for hypertension, excess weight, abnormal lipids, insulin resistance, carotid atheromatosis and death from diabetes or heart disease have been reported in this population. Studies investigating an association between androgenetic alopecia and metabolic syndrome have yielded conflicting findings. Distinct guidelines for the detection and prevention of cardiovascular disease in individuals with androgenetic alopecia have not been established. In addition to the traditional risk factors for developing cardiovascular disease, included in the definition of the metabolic syndrome, several skin diseases have recently been shown to be markers of conditions relating to the patient's overall health. Physicians should be aware of the possible connection between relatively frequent skin diseases, such as psoriasis and hair growth disruptions, including androgenetic alopecia and female pattern hair loss and cardiovascular disease. This review is concentrated on the association between insulin resistance, type 2 diabetes, abdominal fat, cardiovascular disease and hair growth disruptions as an early indicator of these underlying conditions. We have investigated the importance of robust primary clinical treatment measures to address the manifestation of hair loss due to a disruption caused by metabolic syndrome as an effective means to alleviate further stress induced hair loss, which can exacerbate the underlying cause.

## Introduction

### Hair loss-related disease such as androgenetic alopecia

Androgenetic alopecia (AGA) is a chronic immune-mediated inflammatory skin disease characterised by uncontrolled proliferation of keratinocytes, activated dendritic cells, release of proinflammatory cytokines and the recruitment of T cells to the skin. Androgenetic alopecia affects both sexes [1,2]. The condition is characterised by the progressive loss of terminal hairs on the scalp in a characteristic distribution. In men, the anterior scalp, mid scalp, temporal scalp and vertex of the scalp are typical sites of involvement. 'Male balding' and 'male pattern hair loss' are additional terms used to refer to this condition. In women, the condition is characterised by a general decrease in the hair's volume, a noticeable widening of the mid-line part and/or a see-through appearance on the top of the scalp. The term 'female pattern hair loss' (FPHL) is used to refer to this condition.



In humans, all terminal hair follicles are present at birth and follicular growth occurs in a cyclical manner—often referred to as the hair growth cycle. The growth cycle for follicles on the scalp consists of three main phases; anagen, catagen and telogen [1,2]. Roughly 5 million hair follicles cover the human body at birth [2], and no additional follicles are formed after birth. However, the size of the follicles can change over time, and the hair growth cycle can be disrupted—often due to the influence of androgens. The prevalence of male androgenetic alopecia varies by age and race. Approximately 30 percent of Caucasian men will develop androgenetic alopecia by age 30, 50 percent by age 50 and 80 percent by age 70 [3]. Signs of androgenetic alopecia may first appear during adolescence. In one study, 16 percent of 15 to 17-year-old males exhibited clinical evidence of androgenetic alopecia [4]. However, approximately 15 percent of men never develop androgenetic alopecia apart from the typical post-pubertal temporal recession that develops in nearly all men. Female pattern hair loss shares similarities with male androgenetic alopecia, but the susceptibility and rate of development, as well as distribution patterns of the hair loss, are different in the two sexes. Also, the age of onset for FPHL is often later than in men, however, 57% of women aged 80 and above show evidence of FPHL [5].

Androgenetic alopecia is less common in Asian and African-American men than in Caucasians and also expresses later in life in these populations. Estimates indicate that African-American men are four times less likely to develop androgenetic alopecia than Caucasian men [6,7]. A family history of androgenetic alopecia is often present. Whilst a negative history does not exclude the diagnosis, men with a greater number of family members affected by male androgenetic alopecia are at increased risk of developing it [8]. In particular, studies have found a high concordance of balding between fathers and sons [9,10]. For example, a study of 572 men, evaluated in a dermatology clinic for concerns unrelated to androgenetic alopecia, found that young men with balding fathers were more than five times as likely to exhibit androgenetic alopecia compared to young men with fathers without the condition (relative risk 5.5, 95% CI 1.26-23.99) [10].

### **Specifically on metabolic syndrome and hair loss**

Metabolic syndrome (Met S) is characterised by a number of factors; e.g. abdominal obesity, insulin resistance, dyslipidemia and elevated blood pressure [11]. Similar to androgenetic alopecia, systemic inflammation occurs in patients with metabolic syndrome, and the levels of a number of inflammatory markers, such as tumor necrosis factor, are elevated in both.

Metabolic syndrome with all the specified symptoms has for decades been used as a risk indicator for the development of diabetes and cardiovascular disease (CVD), and it has played a central role as a treatment indicator. There are several definitions of the metabolic syndrome; The National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) is the most widely used. Metabolic syndrome is an important risk factor for the subsequent development of type 2 diabetes and/or CVD. Thus, the key clinical implication of a diagnosis of metabolic syndrome is the identification of a patient who needs aggressive lifestyle modifications focused on weight reduction and increased physical activity.

Androgenetic alopecia has been associated with components of the metabolic syndrome, particularly obesity and type 2 diabetes mellitus. These comorbidities are important to recognise because they can lead to increased mortality, especially mortality due to cardiovascular disease [12]. Several factors might explain the existing association between androgenetic alopecia in men, as well as in women, and metabolic syndrome, notably genetics, environmental exposures, such as tobacco smoking, alcohol consumption, psychological stress, physical activity and shared immunoinflammatory pathways. These various factors may act simultaneously to explain the co-occurrence



of AGA and metabolic syndrome, but the mechanism explaining the association remains unclear. Hyperinsulinemia, hyperaldosteronism and chronic inflammation are also some of the commonly blamed culprits for this association.

Elevated insulin levels contribute to the promotion of vasoconstriction and nutritional deficiency in the follicles of the scalp, and it enhances the effect of DHT on follicular miniaturization [13]. Hyperaldosteronism contributes to an increase in blood pressure and also influences the hair receptors negatively, thus favouring progression of alopecia by disrupting the normal function of the hair growth cycle [14]. Microinflammation in the hair follicles in cases of AGA with an increase in proinflammatory cytokines may be a local manifestation of the systemic inflammation, which is associated with a higher risk of Met S in these individuals [15].

The overall prevalence of Met S in correlation with AGA varies from 16.6% to 28% [16,17]. This association has been most commonly found among people beyond the fifth decade of their life [16,18]. The relative risk of getting Met S in correlation with AGA has consistently shown a definite male prevalence [19] except in a single study where females actually outnumbered the males [17]. Family history plays a significant role in particularly those subgroups of AGA who develop cardiovascular disease early on in life [19,20]. It has also been observed that severe AGA itself confers a higher risk of Met S [16] as well as an increased risk of coronary artery disease [21] compared to those with moderate AGA after adjusting for age, family history and smoking status. The cardiovascular comorbidity of AGA is a well-known fact. Leaving aside a few, the majority of studies conducted worldwide have clearly pointed towards a positive association between AGA and Met S.

Recently, this association has been extended to various other dermatological conditions such as psoriasis, skin tags, acanthosis nigricans, lichen planus, systemic lupus erythematosus and even skin cancers. The trend is clearly visible [22-25]. As far as persistent proinflammatory state, oxidative stress and endocrine abnormalities are concerned, many of the chronic dermatological conditions share at least one of these as their pathogenetic mechanisms. Therefore, it is imperative to look for the features of Met S in these cases also. Chronic inflammation is the bridging link between psoriasis and components of the metabolic syndrome. As the exact mechanism by which psoriasis are related to Met S is not yet explained, systemic studies are needed to further our understanding on this topic [22].

### **Current methods for treatment of hair loss**

While dermatologists treat the disruption of the normal hair growth cycle, which is an expression of the underlying cause, they should be alerted to investigate possible metabolic derangements in all such patients so that the true underlying complications can be prevented well in advance. In this multidisciplinary approach to diagnosis and treatment of the hair growth disorder, there should be a focus on the underlying disease as well as its existing and potential comorbidities, which will certainly be more rewarding for the patient as well as the physician. Today, early onset AGA and FPHL are classified as independent risk factors for the development of Met S. Contrary to the silent symptoms, such as high cholesterol, high blood glucose and hypertension, alopecia is very easy to detect and relevant follow-up activities can immediately be conducted with respect to the diagnosis. Microinflammation in hair follicles in AGA with an increase in proinflammatory cytokines may be a local manifestation of systemic inflammation, which is associated with higher risk of Met S in these individuals [15].

As mentioned earlier, it is important to investigate the different risk factors for Met S in early onset AGA and FPHL either through dietary interventions or by pharmacological treatments. A typical pharmacological combination could include statin and an antihypertensive as a start. Treatment of AGA and FPHL should be started



as soon as possible after the hair growth disruption occurs, especially in women. Such disruptions can lead to, and increase, hair loss due to stress and cortisol-induced hair growth disruption, which can in turn exacerbate the condition [26], if not addressed correctly. Furthermore, the negative image perceptions mean that affected individuals are often highly motivated to seek treatment for the hair loss [27].

### Prospective directions

A number of treatment options for hair loss are available, and the choice has to be based on careful consideration in respect to interactions with other ongoing medical treatments prescribed for the underlying cause. As far as we have been able to establish, there is no evidence that the treatment of AGA or FPHL has a beneficial effect on the treatment outcome of concomitant cardiovascular disease. However, there is evidence that stress can aggravate or accelerate the underlying condition as well as the initial hair loss.

Recently, a paper was published suggesting that a specific first line proteoglycan therapy Nourkrin® with Marilex®, can be a key element of hair follicle growth control [26]. The hair growth cycle is controlled by a dialog between mesenchymal and epithelial compartments. As the activity of diffusible factors, such as growth factors and morphogens, can be modulated by glycans, their possible role and interaction in hair growth control must be taken into account. A number of well-written papers have been published on glycans, more specifically proteoglycans, and the hair follicle since the early 1990s [29-34]. Unfortunately, this has had very limited effect on the therapeutic approach of treating hair growth problems with glycans. The focus of most health care professionals has regrettably remained mainly on the traditional pharmacological drugs registered in most countries for the treatment of androgenetic alopecia, namely, minoxidil and finasteride.

A certain naturally based supplement classified as a proteoglycan replacement therapy Nourkrin® with Marilex®, has become known for its effective anagen inducing and prolongation properties. An increase of up to 35.7% in hair count over a six month period in a double-blind placebo-controlled trial has been demonstrated and reported [35,36]. Furthermore, the studies showed a decrease in the number of vellus hairs along with an increase in overall hair number. A decrease of this type of hair demonstrates a decrease of telogenic hairs and as a consequence, an increase of the number of anagenic hairs; a clear indication that anagenic hairs have replaced telogenic hairs.

### Conclusion

The reduction of risk factors for CVD includes treatment of hypertension, cessation of smoking, glycemic control in patients with diabetes and lowering of serum cholesterol, according to recommended guidelines. Questions have been raised as to whether the metabolic syndrome, as currently defined, captures any unique pathophysiology implied by calling it a 'syndrome', and whether metabolic syndrome confers risk beyond its individual components. The critical weakness of the current metabolic syndrome construct is that treatment of the syndrome is no different than the treatment of each of its components.

As discussed above, a number of skin diseases, e.g. psoriasis, androgenetic alopecia and female pattern hair loss, have been associated with metabolic syndrome or its individual components. Therefore, it is essential that the treatment of hair loss that could be associated with metabolic syndrome is twofold; the treating physician should always consider whether any existing hair loss could be an indicator of metabolic syndrome – or any related conditions. Likewise, it is important to treat the hair loss on an equal footing with lifestyle related treatments in relation to the metabolic syndrome to prevent any additional stress and cortisol-induced hair loss.



When deciding on a treatment to address androgenetic alopecia and female pattern hair loss, it is vital to avoid interactions with any ongoing medical treatments. A naturally based, side effect free proteoglycan replacement therapy Nourkrin® with Marilex® has been shown to be an effective treatment for anagen induction and prolongation. It is an efficacious treatment for hair loss associated with a number of medical conditions, including metabolic syndrome.

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