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Review Article

Metabolic Syndrome, Cardiovascular Disease and the Hair Growth Cycle: Addressing hair growth disruptions using Nourkrin® with Marilex® as a proteoglycan replacement therapy: A concise review

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Abstract

Alopecia is associated with an increased risk of coronary heart disease, and it appears that there is a relationship between the degree of hair loss and the risk of coronary heart disease, meaning, the greater the severity of alopecia, the greater the risk of coronary heart disease. Alopecia is also associated with an increased risk of hypertension, hyperinsulinemia, insulin resistance, metabolic syndrome as well as elevated serum total cholesterol and triglyceride levels. It has not been definitively established whether patients with androgenetic alopecia have a higher cardiovascular risk or prevalence of metabolic syndrome, and results of recent studies indicate that androgenetic alopecia patients do not show differences in insulin resistance or the prevalence of metabolic syndrome. However, androgenetic alopecia patients do show a higher cardiovascular risk, characterised by increased inflammatory parameters and Lp(a) levels. Data collected from female populations are scarce, but it would be interesting to extend our clinical knowledge with this type of data to further our understanding of the connection between androgenetic alopecia, metabolic syndrome and cardiovascular risk. The divergence in results from different studies done in this context may simply be a result of the composition of the study populations with respect to age, gender, severity of alopecia, sample size and perhaps ethnicity. In this connection, a large group of androgenetic alopecia patients is necessary, including different representative groups and varying severities of alopecia. Furthermore, it is recommended that all women and men with androgenetic alopecia be thoroughly examined and that lifestyle changes are made early on to reduce the risk of various problems associated with metabolic syndrome, since androgenetic alopecia can be considered an early marker of metabolic syndrome.

Introduction

The association between metabolic syndrome and androgenetic alopecia

Androgenetic alopecia (AGA) is a hair loss condition characterised by specific patterns of hair loss, depending on the circulating androgens in genetically predisposed women and men. In women, the incidence of AGA is only 2-5% by the age of 50, but the ratio rises to 40% by the age of 70, however, AGA affects 80% of men by the age of 70. Although, the main aetiological factors are the same, phenotypic manifestations are different in women and men. Men usually have bi-temporal and vertex hair loss leading to complete baldness. In women, the frontal hairline is usually preserved and complete baldness does not occur [1].

The term 'metabolic syndrome' (Met S) covers a group of metabolic disorders, such as glucose intolerance, insulin resistance (IR), central obesity, dyslipidemia and

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hypertension, associated with an increased risk of cardiovascular disease [2]. Several studies have investigated the relationship between AGA and Met S, as well as IR, with conflicting results [3-9].

The link between AGA and Met S has so far not been clarified. However, two hypotheses have been proposed; firstly, both AGA and cardiovascular disease are related to an excess of androgens and, secondly, hormonal changes such as hyperandrogenism may play a role in the development of AGA and hypertension [10]. One study found a relationship between AGA and IR, but not with Met S, in 50 male patients with grade ≥3 AGA [4].

The influence of insulin on androgenetic alopecia

The mechanism action of insulin on AGA is not clear, but it has been suggested that insulin may be an important factor in the pathogenesis of AGA as it can cause vasoconstriction and nutrient deficiency. It may also be of influence because it enhances the effects of testosterone [5]. Insulin and insulin-like growth factor-1 may enhance dihydrotestosterone (DHT) levels by inducing 5α-reductase activity in obese patients [11]. A study noted that IR might be a pathophysiological mechanism, or enhancing factor, in early AGA [6], and an additional study found that some parameters associated with IR were significantly increased in 342 female AGA patients [7].

For several decades, it has been known that a number of risk factors, including hair-grooming practices, chemotherapy and genetics, can affect hair loss [12-14]. For the first two risk factors, the hair loss is normally reversible with hair growth returning to normal once the risk factors have been removed.

In recent years, it has been hypothesised that hair loss can be linked to Met S, including prediabetes and/or diabetes [15]. Metabolic syndrome covers a number of medical disorders that increase the risk of developing cardiovascular disease and diabetes when occurring together. Some studies have shown the prevalence in the U.S. to be an estimated 25% of the population - and the prevalence increases with age.

Growing clinical evidence documents the relationship between Met S and hair loss, however, few studies are concerned with the association between hair loss, Met S, its components and diabetes. In a community-based study, a significant association was found between AGA and the presence of Met S, as well as Met S components, after controlling age, family history of AGA and smoking status [16], and in a population-based study, the coincidence of AGA and diabetes mellitus type 2 was found to be significantly higher than other environmental and medical factors in patients with AGA [6]. Lastly, in a recent case, the control study patients with AGA had a significantly higher hyperglycemia (≥110mg/dl) ratio (39.1%) than controls (12.5%) [17].

It has been hypothesised for quite some time that prediabetes, diabetes or/and metabolic syndrome can lead to hair loss and/or thinning. Diabetes is often associated with atherosclerosis, where the thickening of blood vessel walls means that the blood vessels narrow, which can occur in blood vessels all over the body, including the skin. Narrow blood vessels mean less oxygen, which causes symptoms such as shiny and thickened skin as well as hair loss. The hair loss is not limited to any specific area of the body. In the case of circulatory impairment in the legs, hair loss can often be seen on the legs.

There is growing evidence on the relationship between prediabetes and a worsened metabolic profile, meaning, patients admitted to the hospital with hair loss should be screened for both prediabetes and diabetes mellitus [18].

Gender and genetic hair loss in relation to metabolic syndrome

Quite recently, a study was published including 3,408 Korean subjects; 1,701 women and 1,707 men with AGA. The degree of hair loss was assessed using the

Norwood classification for men and Ludwig classification for women. Information on Met S components and other risk factors were also collected. When each component of Met S was considered individually, the association between AGA and all five components of Met S (waist circumference, triglycerides, high-density lipoprotein–C, blood glucose and blood pressure) was not statistically significant. When multiple regressions were used to adjust for age, family history and smoking, there still was no significant association between the prevalence of Met S and moderate to severe AGA in the male group. On the contrary, a statistically significant association was noted between the prevalence of Met S and AGA in the female group [19].

The analysis of AGA and the prevalence of Met S in this large Korean population cohort demonstrated quite different findings compared to previously reported studies. The different results in relation to gender suggest that different mechanisms that have not yet been defined may influence female and male AGA.

In 2016, a study of Egyptian women demonstrated a significant association between Met S and Female Pattern Hair Loss (FPHL). Women with FPHL, particularly with an increased waist circumference or hypertension, should be screened for Met S criteria for early identification and management of the syndrome [20].

The conclusion of the clinical studies performed so far is that there most likely is a relationship between metabolic syndrome and androgenetic alopecia. Whether this is different in the two genders has to be investigated further before a conclusion can be drawn. Ethnical differences might also be taken into consideration.

Addressing and managing metabolic syndrome and its components, including hair loss

The normal procedure is that Met S in patients is detected by a routine check by a physician, and the parameters concentrated on are blood pressure, lipids and glucose combined with body weight. Mortality risk of coronary artery disease after adjustment for conventional cardiovascular risk factors is around three times higher in patients with Met S [21]. Different groups, such as the National Cholesterol Education Program's Adult Treatment Panel III, the World Health Organization and the European Group on Insulin Resistance, agree on the essential components of Met S with minor differences in details and criteria. Out of all of these, the most commonly and worldwide used criterion is the one proposed by the National Cholesterol Education Program's ATP III. It requires the presence of at least three of the following [22]:

Abdominal obesity: Waist circumference: ≥ 102 cm in men or ≥ 88 cm in women

Elevated triglycerides: ≥ 150 mg/dl

Reduced high-density lipoprotein (HDL) cholesterol: < 40 mg/dl for men or < 50 mg/dl for women

Elevated blood pressure: ≥ 130 mmHg systolic or ≥ 85 mmHg diastolic

Elevated fasting blood glucose: ≥ 110 mg/dl

It has been found that the cardiovascular risk conferred by Met S is higher than the individual components and hence, it is important to study the association of certain diseases with Met S as a whole [23].

In many countries, the younger part of the population ≤ 40 years does not attend routine checks, and latent Met S diagnoses are not detected as early as they could have been and as a result, no treatment of the various risk factors are initiated. In many countries, the Met S problems are approached with dietary changes and later on with pharmacological treatments.

The prevalence of Met S has increased in the last few years throughout the world. Psoriasis has consistently been associated with Met S and its various components. However, the association is no longer limited to psoriasis alone. Various dermatological conditions, such as lichen planus, androgenetic alopecia, systemic lupus erythematosus, skin tags, acanthosis nigricans and even cutaneous malignancies, have been associated with this syndrome. Though chronic inflammation is thought to be the bridging link, the role of oxidative stress and endocrine abnormalities have recently been proposed in bringing them together [24].

Microinflammation in the hair follicles and an increase in proinflammatory cytokines in relation to AGA may be a local manifestation of the systemic inflammation that is associated with an increased risk of Met S in these individuals [25].

As mentioned earlier, it is important to investigate the different risk factors of Met S in early onset AGA or FPHL, and interventions can be done either through dietary changes or pharmacological treatments. A normal pharmacological combination could include statin and a hypertensive as a start.

Addressing androgenetic alopecia and/or female pattern hair loss

A treatment of AGA and/or FPHL should also be started. A number of treatment options for hair loss are available, but the treatment choice should be based on thorough consideration to avoid interactions with other ongoing medication. As far as we know, there is no evidence that the treatment of AGA or FPHL has a beneficial effect on the treatment outcome of concomitant vascular disease. However, the negative image perception means affected individuals may be highly motivated to seek treatment for the hair loss [26]. Furthermore, the added stress of experiencing hair loss could worsen the initial hair loss due to the production of cortisol [27] as well as impact the individual's general health and, therefore, negatively influence the underlying condition.

Recently, an interesting paper was published [28] suggesting that glycans are key elements of hair follicle growth control. The hair follicle life 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 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].

However, this has had very limited effect on the therapeutic approach of treating hair growth problems with proteoglycans. Focus has mainly been on the traditional pharmacological drugs registered in most countries for the treatment of androgenetic alopecia, namely, minoxidil and finasteride.

A specific natural supplementation, classified as a proteoglycan replacement therapy, Nourkrin® with Marilex®, has been demonstrated to be effective for anagen induction and prolongation. An increase of up to 35.7% in hair count over a 6-month period in a double-blind placebo-controlled trial have been demonstrated and reported [35-39]. Studies have also shown a decrease in the number of vellus hairs and an overall increase in number of hairs. A decrease of vellus hairs demonstrates a decrease of telogenic hairs and as a consequence, an increase in the number of anagenic hairs, which indicates that anagenic hairs have replaced the telogenic hairs. This indicates that the anagen induction of the proteoglycan replacement therapy has had a significant and measurable effect on the hair growth.

Conclusion

The association between metabolic syndrome and early onset androgenetic alopecia is clear in many studies, and this may contribute to clarify the predisposition

of patients with androgenetic alopecia developing cardiovascular disease. Early screenings and intervention for the development of metabolic syndrome and its components in patients with early onset alopecia may prevent the development of cardiovascular disease, which is valid for both women and men. It is necessary for dermatologists to expand their attention beyond skin pathology not to miss a major opportunity of motivation for the patients to agree to dietary changes, metabolic evaluations and interventions in order to improve the patients' health in an attempt to prevent an escalation of the condition.

The papers published on proteoglycans and their influence on hair follicle growth within the past three decades further suggest that a specific proprietary proteoglycan replacement therapy, Nourkrin® with Marilex®, is a viable treatment option for hair loss types associated with metabolic syndrome and its different components. The treatment of the components of metabolic syndrome is vital in order to improve the condition and avoid a worsening of the patients' health. Efforts should be made from all sides to diagnose possible latent cases of metabolic syndrome; and in cases with associated androgenetic alopecia or female pattern hair loss, these symptoms should be addressed on an equal footing with other lifestyle changes, such as dietary changes, and other interventions to avoid progressing hair loss and to give the patients a sense of control and improved life quality, while decreasing the stress associated with hair loss and thereby additional, unnecessary stress that could influence the patients' health.

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