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Systematic Review

The Role of Sulfotransferase in Predicting and Enhancing Minoxidil Response for Androgenetic Alopecia: A Systematic Review

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Abstract

Androgenetic alopecia affects 50% of the males, most commonly called as male pattern hair loss. Sulfotransferase is a xenobiotic metabolizing enzyme in hair follicle. Minoxidil, a pro-drug converted to minoxidil sulfate by this enzyme. Minoxidil sulfate causes vasodilation, which helps in increasing the flow of oxygen and nutrients to the hair follicle. This study is aimed at assessing the role of sulfotransferase in predicting the response of minoxidil in patients with AGA. The activity of sulfotransferase enzyme in the hair follicle predicts the response to minoxidil response with sensitivity varying from 93 to 100% and a specificity varying from 71 to 83%. Using preparations containing tretinoin along with minoxidil has shown increased and better response, as it upregulates the sulfotransferase enzyme.

Keywords: Minoxidil, Sulfotransferase, AGA, Male Pattern Hair Loss.

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Introduction

Androgenetic alopecia (AGA) also known as male pattern hair loss is a common condition affecting nearly 50% of males. [1] The US Food and drug administration approved topical medication for AGA is topical minoxidil, 2% lotion for females and 5% lotion for males. Sulfotransferases are xenobiotic metabolizing enzymes expressed in large numbers in human liver, but also in other tissues such as hair follicle. Sulfotransferase catalyses the process of sulfonation, which involves the transfer of sulfonyl group to a hydroxyl group. Sulfonation in majority of cases is considered as detoxification pathway, converting into more water soluble metabolites and thus facilitating their excretion.

Types of sulfotransferase enzyme: In humans 3 families of Sulfotransferases (SULTs) are identified, namely SULT1, SULT2, SULT4. Broadly they are classified into 2 groups

1. Membrane bound SULTs: These are located in the golgi apparatus of the cell. Involved in sulfation of peptides, proteins, lipids, glycosaminoglycans.
2. Cytosolic SULTs: these are involved in metabolism of xenobiotics and endogenous substrates like bile acids, steroids, drugs [2]

This article will focus on sulfonation of minoxidil and its significance in the management of AGA

Sulfonation of minoxidil: Minoxidil is a pro-drug, and is converted to active component, minoxidil sulphate by the enzyme sulfotransferase (SULT1A1) present in the outer root sheath of the hair follicle.

The activity of sulfotransferase enzyme varies among individuals. Individuals with higher sulfotransferase activity show better results compared to individuals with lower sulfotransferase activity. This variation occurs due to polymorphism in the coding regions of sulfotransferase. [3] Assessing the activity of this enzyme can aid in foreseeing response to minoxidil among patients. It is believed that a low level of sulfotransferase (less than 0.4 OD405 (Optical density)) leads to decreased response to topical minoxidil. The sensitivity and specificity of this test to predict responders to minoxidil is 95% and

73% respectively. [4] It also is considered to have an accuracy of 96% in ruling out non-responders to topical minoxidil. [1] The test holds true for AGA patients from the Indian subcontinent as well. [5]

And it has been found that the level of follicular sulfotransferase enzyme levels remains unchanged throughout even upto 8 weeks post therapy. This suggests that after therapy, responders do not develop low enzyme levels nor do non-responders convert into responders. [6]

Aim: To assess the role of sulfotransferase in predicting the response to minoxidil.

Material and Methods

Data was collected from peer reviewed journals, health database including pubmed, Cochrane Database of systematic Reviews. This study is a systematic review of articles involving sulfotransferase in AGA. Total of 40 articles were analysed for this review. Study included those articles that involved sulfotransferases role in assesing the response to minoxidil in AGA. Studies lacking peer review, focusing only on other treatment modalities were excluded from the study

Observation and Results

Various authors studied the sulfotransferase activity in the plucked hairs with intact bulb to study the efficacy of topical minoxidil (Table 1). In these studies sulfotransferase assay was performed as reported by Goren et al 2014. In the assay the plucked hairs are collected along with intact bulb.

Hairs were trimmed at 1cm length and suspended in 100 µL of assay solution (50mM phosphate buffer with pH of 8, 5 mM potassium p-nitrophenyl sulfate, 20 µM adenosine 3′,5′ diphosphate, 100 µM minoxidil and 5 mM MgCl2). Hairs are incubated in assay solution for 24 hours. Hairs are removed and the optical density at 405 nm (OD405) was determined with a using a single scan and 1 cm path length. [4]

Table 1: Various studies on assessing sulfotransferase assay

Sl No.	Author	year	Methodology	Results
1	Sharma et al [7]	2019	Twenty patients were enrolled. At baseline 10 hairs were plucked from the target area. Hairs were analysed using Minoxidil response test (MRT). Pt was instructed to apply tretinoin 2mg/cm^2 over the target area for 6 days. On 6th day 10 hairs were plucked and the results were compared	Following treatment 43% of initially nonresponders were converted to responders
2.	Roberts et al [8]	2014	Twenty one patients were enrolled. Among them 15 were minoxidil responders and 6 were non responders	The activity of sulfotransferase enzyme in the hair follicle predicts the response to minoxidil response with sensitivity of 93% and a specificity of 83%
3.	Goren et al [4]	2014	Thirty four patients were enrolled. All patients were on minoxidil monotherapy for atleast of 6 months	The activity of sulfotransferase predicts the response to topical minoxidil with sensitivity of 95% and a specificity of 73%
4.	Goren et al [1]	2015	Fifteen patients were enrolled. 8 – males, 7 – females	The activity of sulfotransferase predicts the response to 5% topical minoxidil with a sensitivity of 100% and a specificity of 71%
5.	Chitalia et al [5]	2018	One hundred and twenty patients were enrolled.	40.8% had low sulfotransferase activity. 49.3% of men had low levels of sulfotransferase Activity, compared to 26.6% of women. There was no association with age, family history, duration of alopecia, grade at the time of diagnosis
6.	Ramos P M et al [3]	2020	Eight female patients were enrolled. They used 5% minoxidil for 24 weeks. Sulfotransferase assay was performed at the end of 24 weeks	The activity of sulfotransferase enzyme in the hair follicle predicted the response to minoxidil response
7.	Ramos P M et al [9]	2020	Thirteen female patients were enrolled. They were treated with 1mg oral minoxidil for 24 weeks. Sulfotransferase assay was performed	Results show that outer root sheath sulfotransferase activity predicts the clinical response.

Discussion

All the studies support that the activity of sulfotransferase in the outer root sheath predicts the therapeutic response to minoxidil. The patients not responding to conventional topical minoxidil therapy can be treated by:

Using minoxidil sulfate based formulations in patients with low follicular sulfotransferase enzyme has shown better efficacy than conventional minoxidil preparations. [10,4,11]

Using preparations containing tretinoin along with minoxidil has shown increased and better response. This has been attributed to increased percutaneous absorption of minoxidil facilitated by tretinoin. [12] Tretinoin also leads to upregulation of follicular sulfotransferase enzymes in non-responders thereby increasing the conversion into minoxidil sulfate which is the active metabolite that promotes hair growth. [7] It has also been proved that once daily application of the combination preparation of 5% minoxidil and 0.01% tretinoin, is equally efficacious to twice daily application of 5% minoxidil only containing preparation. [12]

Receptors such as retinoic acid receptor (RXR), pregnane X receptor (PXR) and constitutive androstane receptor (CAR) have been reported to regulate the function of sulfotransferase enzyme.

Tretinoin (all-trans retinoic acid) is an agonist of RXR. RXR forms dimmers with other receptors and upregulates sulfotransferase. [7]

Oral minoxidil: Topical minoxidil needs sulfotransferase enzyme in the outer root sheath for conversion to active metabolite for therapeutic response whereas oral minoxidil does not require this pathway as its converted into active metabolite through hepatic sulfonation. [5] Therefore, more studies are required to understand the efficacy of oral minoxidil in patients with low sulfotransferase activity.

Conclusion: The article stresses important issues which are of practical importance on a topic which has not been covered in any recent Indian review in recent times and is of value in the practice of trichology. Sulfotransferase assay can be used to predict patient outcome even before the start of therapy. This can help in pursuing other modes/tretinoin combination lotions in non-responders without waste of time and money.

Research in to methods or drugs aimed at enhancing or by passing this step is needed.

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