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# Title page

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# Comment on "Androgenetic alopecia is associated with increased scalp hardness":Role of Phosphodiestrase inhibitors?

Dear Editor,

We read with great interest a study by Chen et al.[1], published in the *Journal of European Academy of Dermtology and Venererology*. The authors hypothesized that androgenetic alopecia (AGA) may be associated with scalp hardness. That hardness at the frontal and vertex scalp was significantly higher in AGA male patients. Scalp hardness at the frontal and vertex scalp was also higher in subjects with higher AGA severity. Transforming growth factor β1 (TGF-β1) plays a role in the pathogenesis of AGA and associated scalp hardness.[1]

TGF-β superfamily is an important mediator of tissue repair. Each TGF-β isoform may exert a different effect on wound healing, which may be context- or tissue-dependent. In particular, TGF-β1, the profibrogenic molecule, may

mediate fibrosis in adults' wounds, while TGF-β3 may promote scarless healing in the fetus and reduced scarring in adults.[2]

Administration of oral phosphodiesterase type 5 inhibitor (PDE5) inhibitors, such as 50 mg sildenafil per day for 12 weeks, may be an alternative medical treatment of the plaque of Peyronie's disease (PD), an acquired wound healing disorder affecting the tunica albuginea of the corpus cavernosum.[3]Several cytokines have been implicated in PD pathogenesis, including TGF-β1.[3] Sildenafil treatment also significantly decreased the expression of several pro-fibrotic factors that were upregulated by TGF-β1 treatment in skin fibroblasts of systemic sclerosis.[4]

In their study, Choi et al. noted that cilostazol, a PDE3 inhibitor, could experimentally, promote hair growth by stimulating human dermal papilla cells (hDPC) proliferation, enhancing hair shaft elongation and prolongation of anagen induction in C57BL/6 mice.[5] Later, Choi et al.[6] measured the expression of PDE5A and found that PDE5A mRNA and protein were highly expressed in hDPCs and human hair follicles (hHFs). Sildenafil also increased the mRNA expression of vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF) in hDPCs, which stimulate secretion of these factors, and can promote proliferation of hDPCs. Further, sildenafil may affect perifollicular angiogenesis around hair follicles, and prolong the anagen hair cycle.

Apremilast, a phosphodiesterase 4 inhibitor, showed a significant improvement of extensive, refractory alopecia areata. Furthermore, apremilast significantly reduces TGF-β1-induced fibroblast migration, inhibits dermal fibroblast differentiation into myofibroblasts that is mediated by TGF-β1 in psoriatic patients.[7,8]

TGF-β1 signaling is a critical driver of collagen accumulation and fibrotic diseases but also a vital suppressor of inflammation and epithelial cell proliferation.

We agree with the hypothesis delivered by Chen et al.[1], and we thought that attenuating/ameliorating drugs of TGF-β1 signaling, and its pro-fibrotic activity, such as PDEI may represent a future hope for hair disorders. These drugs/agents can be useful alone or in combination as a therapeutic for disorders with perifollicular fibrosis, such as AGA. Chen et al.'s study[1], though a preliminary, it may pave the way to better understanding of AGA. Further research into drug-delivery, ideal topical concentration or oral dose and frequency, side effects of these drugs are warranted. As per our speculation, PDEI drugs may be a promising therapy for AGA.

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