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REVIEW ARTICLE

COVID-19 Can Exacerbate Pattern Hair Loss and Trigger Telogen Effluvium – The Role of Proteoglycan Replacement Therapy with Nourkrin® in Clinical Treatment of COVID-19 Associated Hair Loss

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Abstract

The unfolding coronavirus disease 2019 (COVID-19) has increased the incidence of several dermatological disorders, including diffuse hair loss. Research revealed an escalated incidence of pattern hair loss (PHL) and telogen effluvium (TE) in COVID-19 patients. Psychological stress, systemic inflammation and oxidative stress are potential culprits. Reduced anagenic expression of proteoglycans is a potential mediating mechanism that connects hair loss to critical health conditions such as COVID-19. Proinflammatory cytokines and stress hormones negatively affect the normal metabolism of proteoglycans, which are known regulators of the hair growth cycle. In this review, we discuss the association between COVID-19 and diffuse hair loss and elucidate the position of proteoglycan replacement therapy (PRT) using Nourkrin® with Marilex® in addressing the dysmetabolism of proteoglycans in COVID-19. PRT with Nourkrin® is a hair loss treatment with 'anti-inflammatory' and 'hair growth cycle normalizing' effects, shown to suppress several proinflammatory cytokines and expand regulatory T-cell lineages *in vivo*. Accordingly, PRT is a potential option for the treatment of new-onset or aggravated PHL in COVID-19 survivors. In addition, bioactive proteoglycans in Marilex®, e.g., decorin and versican, exhibit anagen inducing and catagen suppressing properties, which help to reverse anagen shortening in stress-induced TE. Further clinical investigation of PRT in COVID-19 survivors through controlled trials and real-world studies is warranted. In conclusion, Nourkrin® can be considered as a safe treatment to prevent and treat COVID-19 related PHL and TE.

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Keywords

COVID-19, Pattern alopecia, Telogen effluvium, Nourkrin®, Marilex®, Proteoglycan replacement therapy, Anti-inflammatory agents

Abbreviations

SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2; COVID-19: Coronavirus Disease 2019; TE: Telogen Effluvium; PHL: Pattern Hair Loss; MPHL: Male Pattern Hair Loss; FPHL: Female Pattern Hair Loss; IL: Including Interleukin; TNF-α: Tumor Necrosis Factor α; ROS: Reactive Oxygen Spices; IFN-γ: Interferon γ; MCP-1: Monocyte Chemoattractant Protein 1; IP-10: Interferon Gamma-Induced Protein 10; FHG: Follicular Hypoglycania; PFA: Proteoglycan Follicular Atrophy; PRT: Proteoglycan Replacement Therapy; CXCL2: Chemokine Ligand 2; VEGF: Vascular Endothelial Growth Factor; PTSD: Post-Traumatic Stress Disorder; TGF-β1: Transforming Growth Factor Beta 1

Introduction

Since late 2019, the global public health and wellbeing have been immensely challenged by the outbreak of a new strain of coronavirus designated 'severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)' [1]. This strain of the Coronaviridae family causes an infectious disease in humans known as the 'coronavirus disease 2019 (COVID-19)'. The clinical presentation of COVID-19 varies from an asymptomatic infection to a life-threatening, multiorgan disease. The main target organ of SARS-CoV-2 is respiratory epithelial cells and pneumocytes due to the affinity of the virus to angiotensin-converting enzyme 2 receptors [2].

COVID-19 is reported to increase the risk of a range of significant complications, including pneumonia, acute respiratory distress syndrome, acute liver and/or kidney injury, cardiac complications, prothrombotic coagulopathy, bacterial/fungal co-infections (e.g. mucormycosis), and neurological syndromes [3,4]. Above and beyond, the global pandemic of COVID-19 has taken serious psychological tolls on general public. Even further, this protean disease exposes its victims to yet another, less recognized set of complications: dermatological disorders [5].

An evolving body of literature has associated COVID-19 with primary mucosal, hair, nail and skin complaints, which may precede the classic symptoms of COVID-19 in some cases. Pruritic erythematous rash and/or patchy exanthematous red rash on trunk appear to be the most common cutaneous findings. Acroischemic lesions or "COVID toe", which are micro thrombotic presentations of COVID-19, may occur in both children and adults [5,6]. Hair growth related disorders have also been an important area of concern during the recent COVID-19 outbreak among both clinicians and the public. A web-based evaluation of public dermatologic interests using Google Trends in Italy and Turkey between April and June of 2020 revealed that 'hair loss' was among the most searched dermatology related terms in both countries [7]. A simultaneous rise in public apprehension about hair loss along with the rising number of COVID-19 cases may indicate a connection. It is likely that either the pathogenetic aspects or psychiatric complications of COVID-19 can lead to the appearance or aggravation of hair loss. Conventional treatments of diffuse hair loss in men and women are strictly scarce, particularly in the case of telogen effluvium (TE), and are limited to topical minoxidil and per-oral finasteride. The present review attempts to clarify these pathophysiological connections and discuss a novel therapeutic approach for the prevention and treatment of hair loss in individuals suffering from COVID-19.

COVID-19 and Pattern Hair Loss

Prevalence of pattern hair loss is increased in patients with COVID-19

Clinical surveys conducted in Spain [8,9] and India [10] demonstrated higher rates and severity of pattern hair loss (PHL) in hospitalized COVID-19 patients compared to age-matched, non-infected populations. The first preliminary study that became available was a descriptive study on 41 Caucasian males admitted to hospitals in Spain with a diagnosis of bilateral SARS-CoV-2 pneumonia (mean age = 58 years). 71% of the subjects were diagnosed with significant male pattern hair loss (MPHL) of which 39% had a severe involvement [8]. A follow-up, multicenter study on 175 confirmed COVID-19 patients verified those preliminary findings and reported that 79% (95% CI: 70-85%) of men and 42% (95% CI: 29-55%) of women had significant PHL. These values are in sharp contrast with the expected prevalence rates among age- and race-matched populations. The prevalence of MPHL in a similar white population is expected to be at 31-53%, and that of female pattern hair loss (FPHL) to be at maximum 38% [9,11]. Hence, the data available up to date points to a considerably higher prevalence and severity of PHL among hospitalized COVID-19 patients. Notably, patients with higher stages of hair loss had worse clinical outcomes (use of ventilator and deaths). Some authors proposed the eponym 'Gabrin sign' to refer to the phenomenon of severe baldness in COVID-19 patients with higher risk of unfavorable final outcomes [10]. The association between androgen hyper-sensitivity and more severe COVID-19 may be explained by the fact that both transmembrane protease serine 2 and angiotensin-converting enzyme 2 receptor, which mediate SARS-CoV-2 cell entry, are androgen regulated [12]. However, confirming a causal relationship requires data from larger, controlled surveys in both inpatient and outpatient settings.

Beyond having a positive correlation with the SARS-CoV-2 infection, diffuse alopecia appears to be

an important sequel of COVID-19. A large longitudinal study on 538 COVID-19 survivors and 184 controls was carried out in Wuhan, China, in order to investigate the prevalence and predictors of COVID-19 clinical sequelae. Three to four months after discharge, alopecia was among the most prevalent complains in convalescent COVID-19 patients, reported more commonly by women. Almost half of the female participants started experiencing hair loss after being infected by SARS-CoV-2 compared to no case in the control group. 27% of affected cases experienced alopecia during their hospitalization while 73% first recognized it after being discharged [13]. Due to the timing of symptoms, at least a proportion of the cases with newly-onset alopecia in this study are suspected to have premature or exacerbated FPHL.

In explanation of the observed relationship between PHL and COVID-19, a key role for systemic inflammation as a common underlying pathology is conceivable (elaborated in the next section). This important factor may as well justify higher grades of hair loss in patients with severe COVID-19 as reported by Wambier, et al. [10]. Hypoxemia leading to skin ischemia is another potential pathogenetic factor that connects lung damage secondary to SARS-CoV-2 infection with hair growth impairment. Ex *vivo* and *in-vivo* experiments by Kato, et al. demonstrated significant reductions in hair growth rate, hair shaft size and pigmentation in anagen hairs under ischemia [14].

Systemic inflammation in COVID-19 can exacerbate pattern hair loss

Although PHL in both sexes (i.e., MPHL and FPHL) is traditionally categorized as a non-inflammatory type of hair loss, it is becoming progressively evident that immune driven pathways and inflammation are its inseparable causal elements [15]. Recent attention to the significance of mechanisms beyond androgens in the pathogenesis of MPHL and FPHL has given rise to a 'paradigm shift'. This modern perspective has substantial clinical implications on the choice of treatment depending on the possibility and extent of inflammation/oxidative stress in each individual [16,17]. We propose that immune driven reactions are among the main etiological factors of COVID-19-related diffuse hair loss.

There is direct histological evidence for the involvement of inflammation in PHL. Examination of biopsies from transitional scalp areas of patients uncovered extensive infiltration of mononuclear cells and actively degranulating mast cells within follicular sheaths. Fibroblastic activation in alopecic areas resulted in deposition of collagen and replacement of follicular trichogenic elements by fibrotic sheath residua (fibrous tracts). In addition, soluble materials and cytokines secreted by infiltrating immune cells may also exert deleterious effects on the cyclic activation of papillary cells and stem cell populations [18]. Overproduction of proinflammatory cytokines, including interleukin 1 (IL-1) and tumor necrosis factor α (TNF-α), induces premature catagen, triggers oxidative stress and promotes apoptosis in hair cells. Keratinocytes are shown to respond to chemical stress within minutes by releasing such factors as IL-1, reactive oxygen spices (ROS), prostaglandins and histamine. These diffusible factors potently inhibit hair growth and survival [19]. Oxidative stress in follicular microenvironments, which is a known contributor to PHL, [20] can be triggered by several of the main etiologies of alopecia, e.g., drugs, stress, age and exposure to microbial antigens.

SARS-CoV-2 is a cytopathic virus capable of causing high levels of virus-linked pyroptosis (an inflammatory form of lytic programmed cell death) and vascular leakage in involved tissues. Thus, local and systemic inflammations are pivotal pathogenetic sources of tissue damage and systemic complications in acute and convalescent COVID-19 patients. Cell invasion and disseminated pyroptosis trigger a strong cytokine response boosting the plasma levels of major proinflammatory cytokines: IL-1β, IL-6, IL-2, IL-17, interferon γ (IFN-γ), monocyte chemoattractant protein 1 (MCP-1), interferon gamma-induced protein 10 (IP-10) and many more [21]. It is sensible to conjecture that such an abrupt surge in the circulating level of multiple catagenic cytokines in COVID-19 patients exposes follicular cells to strong inhibitory and disruptive influences. In response, the hair growth cycle becomes disrupted and the gradual process of PHL greatly accelerated. This mechanism explains the appearance of exacerbated hair loss shortly after being infected with SARS-CoV-2 described earlier. Accordingly, inflammation and oxidative stress appear to play determining roles in COVID-19-related hair loss and need to be taken into consideration in our clinical approach. Thus, the frequent oversight of the role of inflammation in PHT as well as the lack of a safe conventional treatment to address this pathology has contributed to the common undertreatment and dissatisfaction of patients.

Proteoglycan dysmetabolism mediates the negative effects of inflammation on hair follicles

Several bioactive proteoglycans are highly expressed in follicular dermal papilla, connective tissue sheath and the bulge area, where fibroblasts and stem cells are accumulated. Along with the multiplication of follicular cells during each telogen-to-anagen transition, the expression of matrix proteoglycans dramatically increases [22]. Evidence denotes that sufficient presence of key proteoglycans throughout anagen is essential for instigating and maintaining a normal hair growth [23,24]. According to a recent study, the expression of certain proteoglycans is significantly reduced in PHL-

affected follicles [25]. This pathologic state is known as follicular hypoglycania (FHG), which can trigger a negative feedback loop of cellular dysfunction and further decline in proteoglycan synthesis. Over time, this hypoglycanic vicious cycle can lead to anagenic undergrowth and follicular hypotrophy and atrophy (miniaturization). The miniaturization and atrophic changes in hair follicles secondary to the influence of FHG is referred to as proteoglycan follicular atrophy (PFA) (for an inclusive discourse on the role of FHG and PFA in hair loss please refers to a review by Wadstein, et al.) [26].

As mentioned earlier, the level of a plethora of proinflammatory cytokines soars in the body of individuals with symptomatic COVID-19. The potent impact of some of these secretory factors on cellular synthesis of proteoglycans is well studied. Major inflammatory cytokines, IL-1 and TNF-α, are reported to act synergistically to inhibit the production of specific proteoglycans in different tissues [27,28]. Further research clarified that the disruptive action of cytokines on proteoglycan metabolism is of a mixed type. For example, IL-1 and TNF-α reduced de-novo synthesis of decorin by 34%, while the expression of biglycan was upregulated [29]. Another important inflammatory cytokine, IL-17, exhibits both *in vitro* and *in vivo* catabolic effects and strongly suppresses the synthesis of proteoglycans [30]. IL-17 is a key player in the pathogenesis of COVID-19 [31]. In addition, immune derived cytokines provoke the expression and activity of matrix metalloproteinases and thereby increase the degradation of proteoglycans [32]. In conclusion, systemic inflammation in COVID-19 can lead to significant 'dysmetabolism' and disturbance of the expression and composition of follicular proteoglycans. Hence, symptomatic COVID-19 can act as a triggering factor that initiates and accelerates FHG and PFA in susceptible scalp hair follicles. This phenomenon shortens the anagen, affects follicular integrity and overall, aggravates the course of PHL. FHG and PFA are suggested to be mechanisms that, at least partly, mediate the negative effects of inflammation on hair growth.

Proteoglycan Replacement Therapy for the Treatment of Pattern Hair Loss in COVID-19 Patients

A novel therapeutic method for diffuse hair loss in men and women is proteoglycan replacement therapy (PRT). This approach is based on oral administration of a selected complex of marine proteoglycans, branded as Marilex® (Pharma Medico Aps, Aarhus, Denmark). Marilex® and its fortified version, Marilex®-M, are the main ingredients of Nourkrin® Woman and Nourkrin® Man oral tablets, respectively. These therapeutics are reach in hair-specific proteoglycans, including versican, decorin and syndecans, with documented hair growth stimulating effects [26]. The starting dosage of both Nourkrin® Woman and Nourkrin® Man is two tablets per day prescribed b.i.d., which can be tapered after 6-12 months.

Per oral PRT using Nourkrin® with Marilex® has been in clinical use for the treatment of PHL for years with promising clinical results [33,34]. This method primarily works by preventing catagen in growing and inducing anagen in dormant hair follicles through the action of its bioactive proteoglycans as comprehensively reviewed by Wadstein, et al. [26]. Alongside those more recognized effects, specialized proteoglycans present in Marilex® are shown to possess *in vivo* anti-inflammatory and antioxidative properties (see below). This unique attribute of PRT is potentially the most relevant in treating COVID-19-related hair loss. Anti-inflammatory effects of PRT may root in the fact that certain matrix proteoglycans are immunomodulatory effectors essential for normal regulation of several immune-related reactions [35]. As an example, a sufficient expression of syndecan 1 and 4 is essential for inhibiting the hyperactivity of T-cells [36,37]. In an *in vivo* model of inflammation, per oral treatment with a cartilage-based proteoglycan formula resulted in attenuation of clinical and histological severity of inflammation. Proteoglycan treatment suppressed IFN-β, IFN-γ, MCP-1 and IL17, all of which are involved in the pathogenesis of COVID-19. Even more, Foxp3+ regulatory T-cells were expanded, while the expressions of IL-6, IL-21 and IL-23 receptors were suppressed in treatment groups [38]. Similar outcomes were obtained after oral administration of a simple proteoglycan compound to a model of systemic inflammation. Treatment suppressed tissue mRNA expression of TNF-α, IL-6 and chemokine ligand 2 (CXCL2) and lowered the proportion of activated macrophages (M1) [39]. Preliminary research provides clues as to some anti-inflammatory effects of PRT may be mediated by its positive influence on gut microbiota. Glycan moieties of proteoglycans are known prebiotic compounds, which can enhance, over time, the population of saccharolytic bacteriae in human colon [40]. This group of bacteriae produces short-chain fatty acids with proven anti-inflammatory effects [41]. Given that Marilex® has a multimolecular and more complex composition than cartilage-based formulas, its anti-inflammatory effects are expected to be of a wider scope and/or higher intensity. Further *in vivo*/clinical research on this topic is warranted.

As mentioned earlier in this paper, hypoxia in COVID-19 patients leaves detrimental effects on hair growth and cycling, which justifies the clinical application of certain proteoglycans with protective effects against ischemic injury, including decorin and biglycan. The cytoprotective efficacy of leucin-rich proteoglycans is documented on cardiomyocytes [42]. Domain V of human perlecan is also shown to promote growth factor signalling toward enhanced angiogenesis

and vascularization, which represents a targeted mechanism to neutralize pathological impacts of cellular hypoxia [43]. Angiogenesis involves the stimulation of endothelial cells by pro-angiogenic signals, such as vascular endothelial growth factor (VEGF), that is also induced by the major hair loss medication, minoxidil [44]. Promoting angiogenesis and protecting the cells from ischemia are regarded important action mechanisms of PRT in treating COVID-19-induced hair loss.

Certain proteoglycans, such as versican, are also part of the intrinsic antioxidant defense system that protects cells from oxidative stress-induced apoptosis. A controlled experiment concluded that stable expression of versican or its C-terminal domain alleviates H_2O_2-induced cellular apoptosis [45]. Putative antioxidative and cytoprotective mechanisms of proteoglycans are proposed to be: 1- Their negatively charged side chains inhibit lipid (per) oxidation by chelating positively charged metal ions; 2- Proteoglycan-bound superoxide dismutase scavengers superoxide anions; 3- Proteoglycans form a pericellular net that interferes with the diffusion of oxidative molecules; 4- Proteoglycans mediate key intracellular redox signaling pathways [46]. Possessing a diverse profile of anti-inflammatory and antioxidant features makes Nourkrin® an attractive option for the treatment of new-onset or aggravated hair loss in patients with a history of COVID-19 or similar inflammatory diseases. In addition, Nourkrin® is well-tolerated and has not been associated with any significant side effects in either clinical trials or real-world practice.

The COVID-19 Outbreak Provoked Stress-Induced Hair Loss

Since its inception, COVID-19 has imposed a pervasive, notorious impact on the public that reached even beyond the frontiers of the infection itself: Psychological stress and anxiety. As reported by the World Health Organization, there has been a spiky elevation in the rates of stress and anxiety worldwide. Mandated life changes and economic insecurity as well as the fear of unknown are important factors that contributed to the psychological burden of COVID-19. The self-isolation and quarantine measures that affect people's usual activities are expected to increase the incidence of depression, anxiety, substance (alcohol and drug) abuse and suicide [47]. All infected patients, healthcare providers and the general public are at increased risk of psychiatric impediments during a global pandemic. Cross-sectional studies reported that 1 in every 4-5 clinicians and one in every three COVID-19 patients suffer from anxiety or mood symptoms. Early research also signified that clinically significant symptoms of anxiety, depression, distress, and post-traumatic stress disorder (PTSD) were present in up to one third of the general adult population from January to April 2020 [48].

Psychological stress is a known etiology of a group of "stress-sensitive" skin conditions, including acute and chronic TE [49,50]. The physiopathological impact of stress depends on its type and timing. Three types of psychological stress have been defined: 1- Positive stress, which is moderate, brief and an inevitable part of a normal life; 2- Tolerable stress that is more intense but occurs infrequently and gives the brain time to recover; 3- Toxic stress, which is strong in magnitude and induces prolonged activation of systemic stress responses including the sympathetic adrenomedullary system. Extended exposure to toxic levels of stress can chronically raise the circulating level of cortisol and catecholamines, which in turn underlie a wide range of disorders such as depression, anxiety, hypertension, autoimmune diseases and cancer [51].

On the scalp, stress is shown *in vivo* to strongly promote premature catagen and intrafollicular apoptosis in hair follicles. TE associated with COVID-19 is likely to be of a 'immediate anagen release' nature with massive loss of club hairs due to multiple anagen terminating signals provoked by the infection [52]. Increased levels of cortisol and catecholamines are reported to alter the hair gross cycle by affecting follicular stem cells and dysregulating the metabolism of follicular proteoglycans [53,54]. In subjects under psychological stress, perifollicular inflammation expressed by clustering of activated macrophages and degranulation of mast cells were noticed [50]. In addition, patients with severe COVID-19 often receive a wide range of medical interventions, e.g., anti-coagulants, that can independently trigger TE. TE is, therefore, responsible for at least part of the incremental rate of hair loss in COVID-19 survivors reported by Xiong, et al. [13], and observed in > 27% of 1100 survivors in a net-based poll [55]. A more specific study confirmed that, although in-person referrals to dermatology clinics declined during the COVID-19 pandemic, the actual incidence of TE was higher compared to pre-pandemic times [56]. This study is in concert with the narrative experience of a plethora of healthy individuals, COVID-19 survivors and dermatologists from different parts of the world posted online since the rise of COVID-19 [55,57,58].

Using Nourkrin® to Treat Stress-Related Hair Loss during the COVID-19 Pandemic

TE occurs as a result of an induced imbalance in the dynamics of the hair growth cycle secondary to a number of triggering factors. These triggers are assumed to shift the equilibrium between anagenic and catagenic pathways in follicular cells and thereby initiate premature catagen. Since bioactive matrix proteoglycans are essential modulators of several of the anagenic/catagenic pathways [59,60], their expression and activity are suggested to be affected in TE [26]. A number of proteoglycans, e.g., versican, have growth factor-like repeats that bind to cell surface proteins and

mediate the activity of anagen inducing pathways such as Wnt/β-catenin [61], and inhibit catagen inducing factors, e.g., transforming growth factor beta 1 (TGF-β1) [62]. Hence, certain proteoglycans appear to be relevant therapeutic targets in TE with potent anagen inducing and prolongation activity, which have also been verified *in vivo* [63].

In individuals who suffered from COVID-19, the intense psychological pressure and massive inflammatory response are plausible triggers for acute/chronic TE [13]. Inflammation per se can act as an independent as well as a mediating etiology. *In vivo* research demonstrated that specific blockage of the master regulator of inflammation, nuclear factor κB, can largely neutralize the effect of stress on hair follicles [50]. This interesting finding suggests that agents with anti-inflammatory properties have a worthy potential to be used in the clinical management of TE associated with COVID-19 pandemic.

In the absence of a conventional therapeutic option, Nourkrin® with Marilex® is deemed relevant in treating acute/chronic TE triggered by COVID-19 or its psychological consequences. This potential stems from two pharmacological properties of Marilex® as described earlier: First, the catagen preventing and anagen inducing effects of specific proteoglycans found in abundance in Marilex®, and second, it's *in vivo* anti-inflammatory properties. Mitigating the impact of inflammatory cytokines and stress hormones on the activity of follicular cells can prevent the emergence of FHG and its resultant premature catagen initiation. On the other hand, enhancing the expression of proteoglycans induces anagen in dormant hair follicles. This dual therapeutic activity has the potential to prevent the progression of hair loss and help accelerate hair regrowth in COVID-19 survivors and non-infected individuals struggling with stress-induced TE. Another factor that deserves consideration is the role of increased cortisol under the conditions of COVID-19 [64]. High cortisol level is connected with increased degradation of matrix proteoglycans and is, therefore, considered a cause of FHG and a disruptor of the hair growth cycle [53]. Augmenting the concentration of proteoglycans by oral PRT with Nourkrin® can minimize the suppressive effects of cortisol in patients with COVID-19.

In summary, both biological and psychological factors play distinct roles in driving TE in COVID-19 survivors. The increased levels of inflammatory cytokines and stress hormones are proposed to be the main culprits behind FHG and anagen shortening in these individuals. PRT with Nourkrin® is a targeted treatment with anti-inflammatory and hair growth stimulating activities with good potential to address stress-induced TE in individuals affected with COVID-19. Given the fact that Nourkrin® is a non-prescription treatment in most countries, PRT can conveniently be implemented in a teledermatology program, which minimizes the risk of infection spread and is proven successful in managing patients with TE in the age of COVID-19 [65].

Future Perspectives

Due to the novelty of the therapeutic use of bioactive proteoglycans for the treatment of primary and secondary hair growth disorders, there remains a wide range of uncharted areas to be explored. Clinical investigation of PRT with increasing dosages of Marilex® in COVID-19 sufferers/survivors with hair loss through controlled trials and real-world studies is of great clinical interest. Both mono-therapy and add-on therapy with Nourkrin® are suggested to be included in future trials. Evaluating the efficacy of PRT for the management of diffuse hair loss associated with other forms of infections also awaits future research efforts.

Conflicts of Interest

The authors declare that there is no conflict of interest and no funding for the preparation of this manuscript has been obtained.

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A non-peer reviewed manuscript of the current paper has been uploaded to a preprint server by the authors prior to publication (accessible at https://osf.io/m7b3j/).

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