Topical steroid withdrawal is a targetable overproduction of nicotinic acid from mitochondrial complex I overexpression

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Background:
Topical glucocorticoids (more commonly termed topical corticosteroids; TCS) are first line therapy for management of numerous skin conditions. Topical Steroid Withdrawal (TSW) is a controversial diagnosis advocated by patients with prolonged TCS exposure who report severe systemic reactions upon treatment cessation. Although the disease may be confused for eczematous disorders or dismissed outright, there have been no systematic clinical or mechanistic studies to either refute or support TSW as molecularly distinct from other dermatopathies. This
study aimed to clinically differentiate TSW symptomatology, delineate abnormal molecular pathways, and investigate potential therapeutic agents.

**Methods:**

A re-analysis of a previous survey encompassing 1,889 patients with eczematous skin disease who either did or did not self-report TSW was performed to evaluate potential TSW distinguishing symptoms. We then conducted a pilot study of 16 patients who fit the proposed diagnostic criteria. We then performed: tissue metabolomics, transcriptomics, and immunostaining on skin biopsies; serum metabolomics and cytokine assessments; shotgun metagenomics on microbiome skin swabs; genome sequencing; followed by functional, mechanistic studies using human skin cell lines.

**Results:**

Clinically distinct TSW symptoms included thermodysregulation, burning, and flushing. Metabolomic and transcriptomic assessments both implicated elevated NAD+ oxidation stemming from increased expression of mitochondrial complex I and conversion of tryptophan into kynurenine metabolites. These abnormalities were induced by glucocorticooid exposure both \textit{in vitro} and in a cohort of healthy controls (N=19) exposed to TCS. Targeting complex I via either metformin or the herbal compound berberine improved outcomes in both cell culture and in an open-label case series for patients with TSW.

**Conclusion:**

Taken together, our results suggest that TSW has a distinct dermatopathology. While future studies are needed to validate these results in larger cohorts, this work provides the first mechanistic evaluation into TSW pathology, and offers insights into clinical identification, pharmacogenomic candidates, and directed therapeutic strategies.
Keywords: topical steroid withdrawal, skin thermo dysregulation, burning rash, loose skin

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