

# Ultradian Monitoring in Adrenal Insufficiency

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## Summary:

Ultradian platform enables ambulatory, tissue-level profiling of steroid hormones, every 20 minutes over 24 hours. We applied this wearable microdialysis platform in patients with primary adrenal insufficiency receiving different glucocorticoid replacement regimens. Compared with healthy reference profiles, patients spent less time within the physiological cortisol range. These findings reveal dynamic treatment mismatches that conventional sparse sampling cannot capture. Ultradian platform provides a route toward precision endocrine monitoring and individualized glucocorticoid replacement.

**Keywords:** Ultradian; U-Rhythm; ambulatory biosampling; tissue steroid profiling; primary adrenal insufficiency.

## Background, Motivation and Objective

Endocrine function is intrinsically dynamic, yet clinical hormone monitoring still relies mainly on sparse blood sampling. In primary adrenal insufficiency [1], loss of adrenal corticosteroid production requires lifelong glucocorticoid replacement therapy [2, 3].

We used the ambulatory U-RHYTHM system [4], a portable microdialysis-based biosampling platform, to capture high-resolution tissue corticosteroid dynamics in patients with primary adrenal insufficiency receiving different glucocorticoid replacement regimens.

## Methods

Forty-one patients with autoimmune primary adrenal insufficiency were studied during treatment with hydrocortisone, cortisone acetate, or modified-release hydrocortisone. Free steroid hormones were sampled by microdialysis from abdominal subcutaneous tissue every 20 minutes over 24 hours using U-RHYTHM under ambulatory real-life conditions, including overnight sampling (Fig 1). Steroids were quantified by ultra-sensitive LC-MS/MS [5] and compared with a healthy reference cohort of 214 individuals.

Time-resolved reference ranges were used to derive dynamic biomarkers, including time in range, time at extreme concentrations, area

under the curve, peak concentration, rate of post-dose increase, and peak timing.

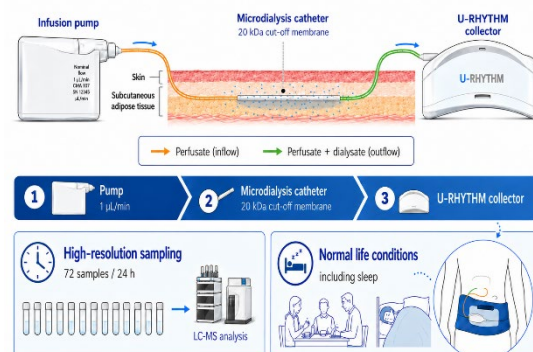


**Fig. 1. Schematic representation of ambulatory microdialysis sampling using U-RHYTHM**

## Results

Ambulatory 24-hour tissue steroid profiling was feasible in patients with primary adrenal insufficiency without disturbing sleep. Across replacement regimens, time within the physiological cortisol range remained low, averaging below 35%, with more than 25% of the day spent at extreme concentrations. The normal pre-awakening rise in cortisol and cortisone observed in healthy individuals was absent. Instead, hormone levels remained very low during the early morning hours and increased only after morning glucocorticoid intake.

Post-dose hormone peaks were delayed and showed altered exposure, transition speed, and morphology compared with healthy controls.

### Conclusions

The U-RHYTHM-based ultradian platform enables wearable, high-temporal-resolution steroid phenotyping at the tissue level under ambulatory conditions. In primary adrenal insufficiency, this approach reveals a persistent mismatch between current replacement regimens and physiological hormone dynamics. This platform provides precision endocrine monitoring and creates the premises for individualized optimization of glucocorticoid replacement therapy.

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