

# Salivary Cortisone is Reduced in Addison's disease Receiving Hydrocortisone Replacement, but Salivary Cortisol Day Curves do Not Differ from Controls

Ross IL<sup>1</sup>, Lacerda M<sup>2</sup>, Pillay TS<sup>3</sup>, Blom DJ<sup>4</sup>, Johannsson G<sup>5</sup>, Dave JA<sup>1</sup>, Levitt NS<sup>1</sup>, Haarburger D<sup>6</sup>, van der Walt J-S<sup>7</sup>

<sup>1</sup>Division of Endocrinology Department of Medicine University of Cape Town South Africa, <sup>2</sup>Department of Statistical Sciences University of Cape Town South Africa, <sup>3</sup>Department of Chemical Pathology University of Pretoria South Africa, <sup>4</sup>Division of Lipidology Department of Medicine, University of Cape Town, <sup>5</sup>Department of Endocrinology Institute of Medicine Sahlgrenska University Hospital University of Gothenburg Sweden, <sup>6</sup>Ampath Laboratories Pomona Gauteng Province South Africa, <sup>7</sup>Astellas Pharma Leiden Netherlands

## Introduction

- Immediate release conventional hydrocortisone and cortisone acetate are the most commonly used replacement therapies in Addison's disease.
- The cortisol concentration profile and overall quality of conventional hydrocortisone replacement has been examined using urine and serum cortisol, plasma ACTH and salivary cortisol, but all measurements have limitations.
- Salivary cortisone measured in spot samples taken at various times after the administration of hydrocortisone has been shown to correlate with simultaneously measured serum cortisol in patients with Addison's disease.
- We previously reported that salivary cortisol concentrations measured by electric chemiluminescence immunoassay in Addison's patients on hydrocortisone replacement were greater than endogenous cortisol concentrations in healthy subjects.
- Salivary cortisone may be a more accurate measure of serum free cortisol than salivary cortisol, since it is less affected by cortisol binding globulin.
- Liquid chromatography tandem mass spectrometry makes it possible to accurately identify and quantify cortisol and other steroids.

## Aim of Study

- To explore the utility of LC-MS/MS in measuring salivary cortisol and cortisone and determining the pharmacokinetic parameters for hydrocortisone and endogenous cortisol production in Addison's disease and controls.
- To explore the correlation of salivary cortisol and cortisone dose in Addison's patients, hypothesising that salivary cortisone may reflect post dose exposure more accurately than salivary cortisol.

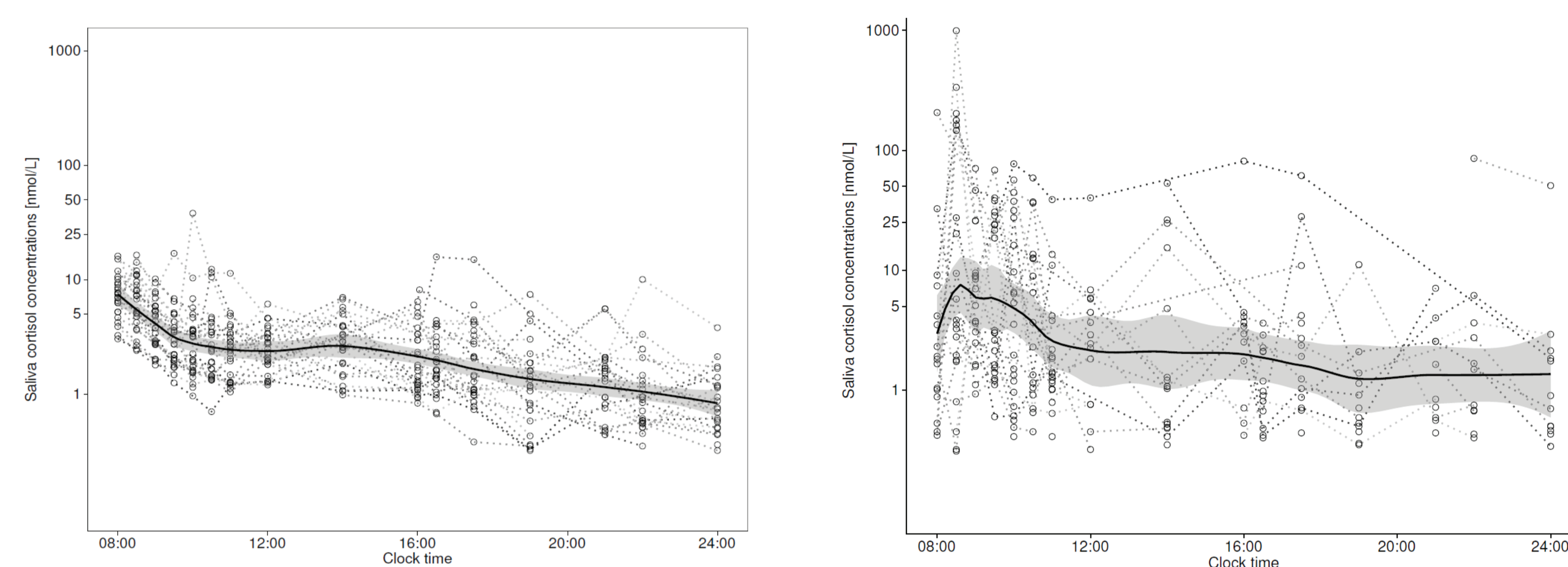
## Methods

- Patients were recruited from the South African Addison study database.
- 12 patients were excluded due to concomitant medication, three patients declined to participate and of the 31 patients who agreed to participate, 25 patients provided sufficient samples for analysis.
- 26 healthy control subjects, mostly medical students were enrolled.
- Saliva was collected at 08:00 (immediately before the first hydrocortisone dose in patients), 08:30, 09:00, 09:30, 10:00, 10:30, 11:00, 12:00, 14:00, 16:00, 16:30, 17:30, 19:00, 21:00, 22:00 and 00:00 (16 samples per participant).

	Controls	Patients
Number	26	25
Age (IQR) years	21 (20-22)	48 (38-63)
Gender Female N(%)	13 (50)	20 (80)
BMI (IQR) kg/m <sup>2</sup>	24.0 (22.6-28.5)	23.8 (21.5-27.3)
Ethnicity		
White N (%)	10 (38)	19 (76)
Mixed ancestry N (%)	2 (8)	5 (20)
Asian N (%)	3 (12)	1 (4)
Black N (%)	11 (42)	0 (0)
Total daily dose of hydrocortisone (IQR) mg		25.0 (20.0-25.0)
Total daily fludrocortisone dose (IQR) mg		0.1 (0.05-0.1)
Total daily dose of hydrocortisone adjusted for body weight (IQR) mg/kg		0.36 (0.31-0.42)
Total daily dose of hydrocortisone adjusted for body surface area (IQR) mg/m <sup>2</sup>		13.9 (11.8-15.2)
Total fludrocortisone dose adjusted for body weight (IQR) µg/kg		1.3 (0.8-1.5)
Total fludrocortisone adjusted for body surface area (IQR) µg/m <sup>2</sup>		0.05 (0.03-0.06)

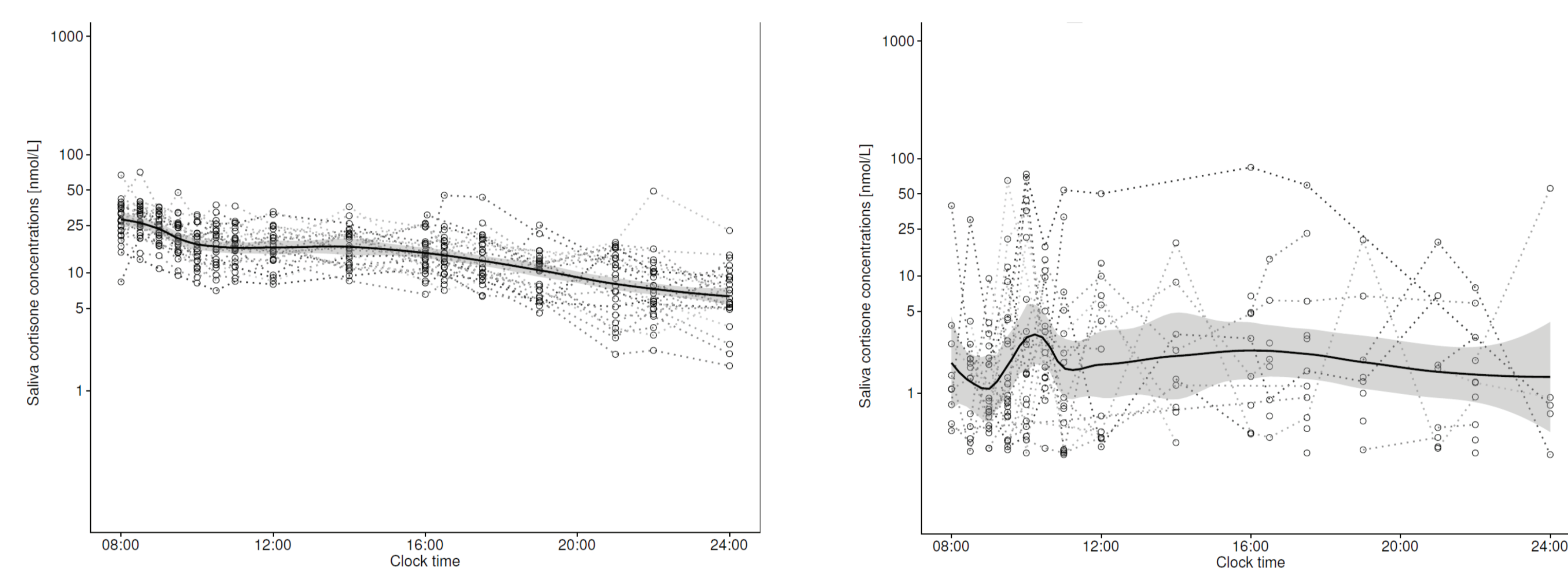
	Cortisol			Cortisone		
	Controls	Patients	p-value	Controls	Patients	p-value
Numbers	26	25		26	25	
AUC	37.49 (27.41-52.00)	55.63 (32.91-151.07)	0.098	227.73 (200.10-280.52)	23.65 (6.10-54.76)	<0.001
C <sub>max</sub> nmol/L	8.96 (6.96-12.23)	32.61 (5.75-146.19)	0.013	33.12 (25.97-39.95)	11.11 (2.91-35.85)	0.002
Time to C <sub>max</sub> hours	0.0 (0.0-0.5)	1.5 (0.5-2.0)	<0.001	0.25 (0.00-0.50)	2.5 (2.0-9.5)	<0.001

## Salivary cortisol in healthy volunteers (a) and patients with Addison's disease (b)



(a) Healthy volunteers

(b) Patients with Addison's disease



(a) Healthy volunteers

(b) Patients with Addison's disease

## Discussion

- Salivary cortisone was approximately 10-fold higher in controls than in patients
- Salivary cortisol AUC in patients did not differ from controls
- Salivary cortisol and cortisone concentrations in patients were highly variable
- Total daily hydrocortisone dose adjusted for body weight or body surface area were highly correlated with the peak cortisol concentration, our data cannot be utilised to base individual dosing adjustments
- We propose that there is higher activity of salivary 11BHS2 in healthy controls than patients
- Alternatively, the bidirectional pathway of 11BHS2 may be down-regulated, whereas 11-beta-hydroxysteroid dehydrogenase type 1 (11BHS1) may be up-regulated in patients

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