Coordinatori:
Prof.ssa Annamaria Colao, Prof. Rosario Pivonello

WEDNESDAY 6 MAY 2015

14.30-15.30 **CURRENT MANAGEMENT OF ADRENAL INSUFFICIENCY: COMPARISON OF EXPERIENCES**
Chairs: **Giorgio Arnaldi, Rosario Pivonello**

NEW THERAPEUTIC PERSPECTIVES OF ADRENAL INSUFFICIENCY
Andrea Isidori, Chiara Simeoli

TREATMENT WITH "DUAL RELEASE“ HYDROCORTISONE IN CONGENITAL ADRENAL HYPERPLASIA

Chiara Simeoli

Dipartimento di Medicina Clinica e Chirurgia, Sezione di Endocrinologia

“Università Federico II” Naples, Italy

J Clin Endocrinol Metab, September 2010

Congenital Adrenal Hyperplasia Due to Steroid 21-Hydroxylase Deficiency: An Endocrine Society Clinical Practice Guideline

Phyllis W. Speiser, Ricardo Azziz, Laurence S. Baskin, Lucia Ghizzoni, Terry W. Hensle, Deborah P. Merke, Heino F. L. Meyer-Bahlburg, Walter L. Miller, Victor M. Montori, Sharon E. Oberfield, Martin Ritzen, and Perrin C. White

UNDERTREATMENT
Adrenal crisis
Hyperandrogenism

OVERTREATMENT
Iatrogenic
Cushing's Syndrome

Physiological cortisol replacement

Evidence

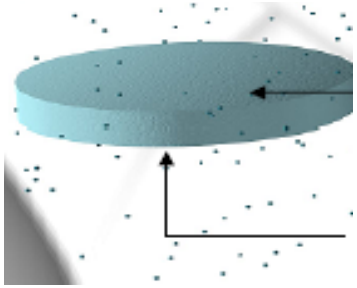
Existing GC therapy is nonphysiological and may contribute to adverse outcomes.

Recommendation

8.3 We suggest the development of new treatment approaches that minimize daily GC exposure and aim to achieve physiological cortisol replacement.

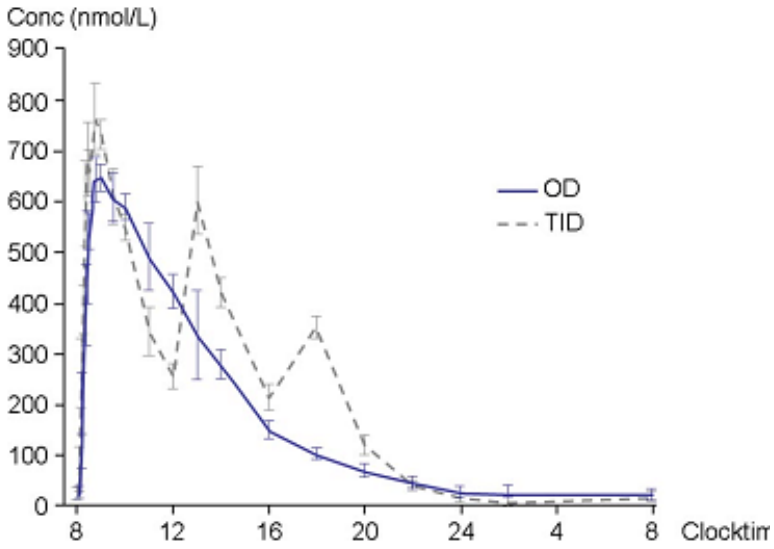
Improved Cortisol Exposure-Time Profile and Outcome in Patients with Adrenal Insufficiency: A Prospective Randomized Trial of a Novel Hydrocortisone Dual-Release Formulation

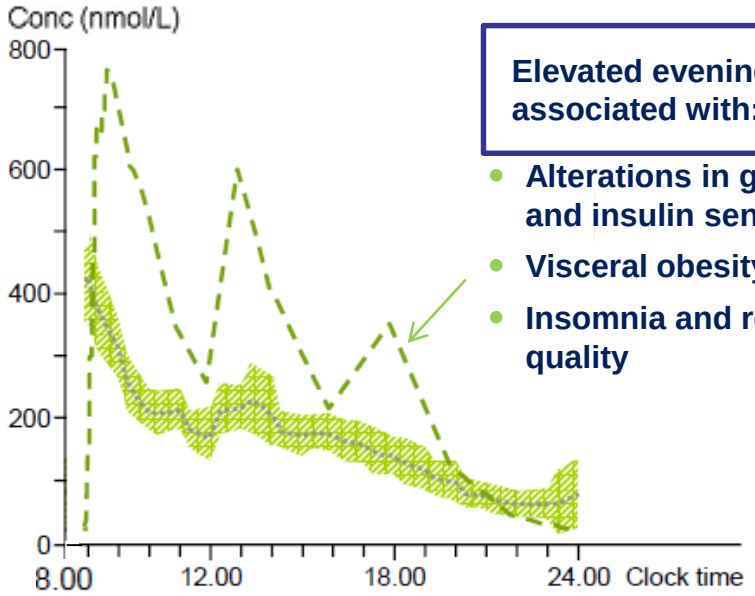
G. Johannsson, A. G. Nilsson, R. Bergthorsdottir, P. Burman, P. Dahlqvist, B. Ekman, B. E. Engström, T. Olsson, O. Ragnarsson, M. Ryberg, J. Wahlberg, B. M. K. Biller, J. P. Monson, P. M. Stewart, H. Lennernäs, and S. Skrtic



Immediate release coating

Extended release core





Elevated evening levels are associated with:

- **Alterations in glucose tolerance and insulin sensitivity**
- **Visceral obesity**
- **Insomnia and reduced sleep quality**

J Clin Endocrinol Metab, February 2012, 97(2):473–481

AIM

The current study aimed at investigating in a cohort of patients with CAH the impact of the switch from twice or thrice daily conventional GCs to once daily dual release hydrocortisone formulation (DR-HC) on:

- Metabolic profile
- Hormonal profile

- Quality of life
- Depression status

- Compliance to treatment

PATIENTS

18 PATIENTS

CONGENITAL ADRENAL HYPERPLASIA

14 Females, 4 Males; 20-29 yrs

- **13 patients** (10F, 3 M) **CLASSIC FORM**
  - 11 Salt Wasting
  - 2 Simple Virilizing
- **5 patients** (4F, 1 M) **NON-CLASSIC FORM**

TREATMENT PROTOCOL

16 pts: **hydrocortisone** (10-40 mg/day; **mean dose 24.06 mg/day**)
2 pts: **prednisone** (6.25-10 mg/day; **mean dose 8.12 mg/day; Eq. HC: 32.5**)

DR-HC (10-40 mg/day**; mean dose 22.77 mg/day)**

11 SW pts: **fludrocortisone** (0.05-0.1 mg/day; **mean dose 0.05 mg/day)**

A 6 and 12 MONTH-FOLLOW-UP

CONTROLS: THE SAME COHORT OF PATIENTS, STABLY TREATED WITH CONVENTIONAL GCS DURING THE 12 MONTHS BEFORE THE SWITCH

METHODS

- Weight (kg)
- Waist Circumference (cm)
- Body Mass Index (kg/m^2)
- Systolic blood pressure (mmHg)
- Diastolic blood pressure (mmHg)

- Fasting Glucose (mg/dL)
- Fasting Insulin(µU/mL)
- Insulin resistance (HOMA-IR)
- Glucose and Insulin during oGTT

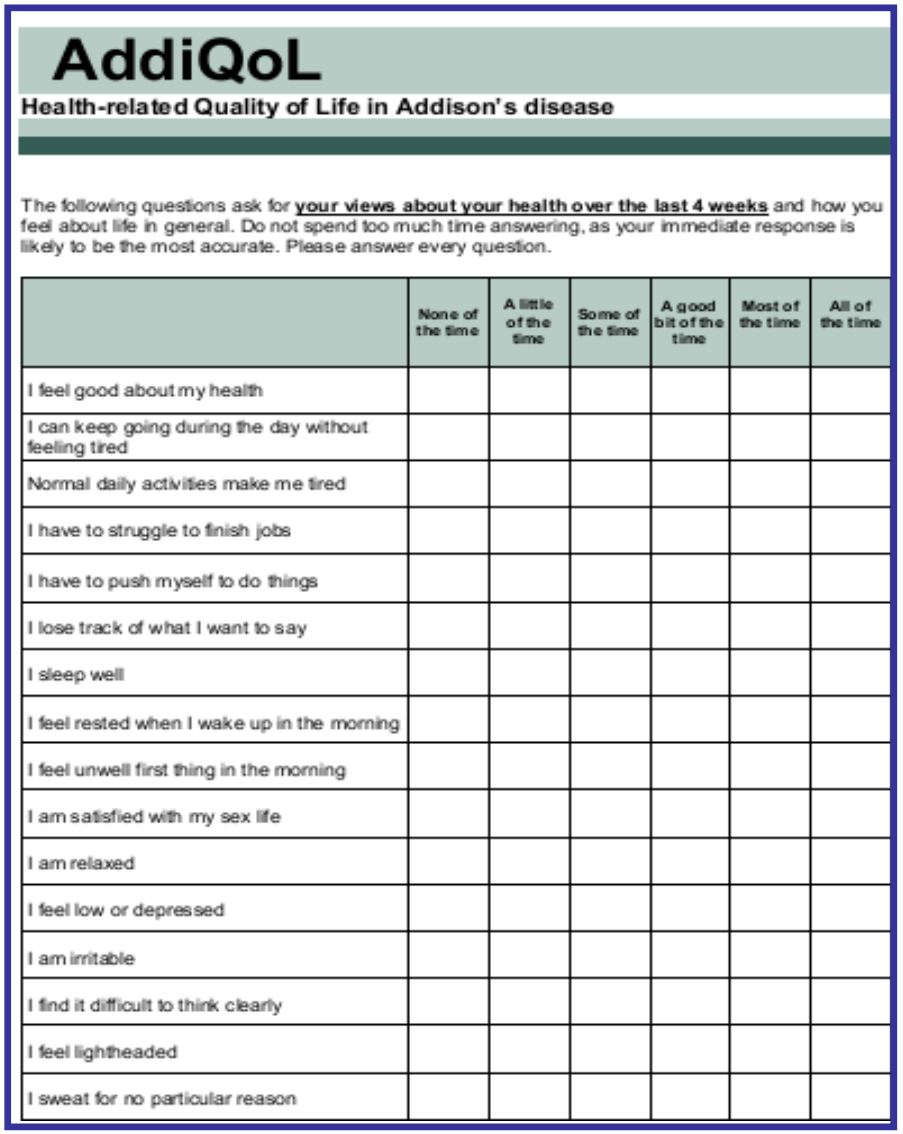
- Triglycerides (mg/dL)
- Total cholesterol (mg/dL)
- HDL-cholesterol (mg/dL)
- LDL-cholesterol (mg/dL)

- Plasma ACTH (pg/mL)
- Serum Cortisol (ng/L)
- Urinary free cortisol (µg/24h)

- Aldosterone (pg/mL)
- Renin (pg/mL)

- 17-OH progesterone (ng/mL)
- Testosterone (ng/dL)
- DHEA-S (µg/dL)
- Δ4-androstenedione (ng/mL)

QUALITY OF LIFE



AddiQoL

Health-related Quality of Life in Addison's disease

The following questions ask for **your views about your health over the last 4 weeks** and how you feel about life in general. Do not spend too much time answering, as your immediate response is likely to be the most accurate. Please answer every question.

	None of the time	A little of the time	Some of the time	A good bit of the time	Most of the time	All of the time
I feel good about my health						
I can keep going during the day without feeling tired						
Normal daily activities make me tired						
I have to struggle to finish jobs						
I have to push myself to do things						
I lose track of what I want to say						
I sleep well						
I feel rested when I wake up in the morning						
I feel unwell first thing in the morning						
I am satisfied with my sex life						
I am relaxed						
I feel low or depressed						
I am irritable						
I find it difficult to think clearly						
I feel lightheaded						
I sweat for no particular reason						

Øksnes M. et al Quality of life in European patients with Addison's disease: validity of the disease-specific questionnaire AddiQol *JCEM* 2012; 97(2):568-76

DEPRESSION STATUS

BECK DEPRESSION INVENTORY (BDI-II)

The Beck Depression Inventory is a self-report measure of the presence and severity of depressive symptoms. It examines an individual's emotional state in the two-week period prior to evaluation.

Raw Scores	Depression Severity
0-13	Indicates minimal depression
14-19	Indicates mild depression
20-28	Indicates moderate depression
29-63	Indicates severe depression

Beck AT, et al. Journal of Personality Assessment 1996; 67: 588–97

TREATMENT COMPLIANCE

Morisky 8-Item Medication Adherence Questionnaire

Question	Patient Answer (Yes/No)	Score Y=1; N=0
Do you sometimes forget to take your medicine?		
People sometimes miss taking their medicines for reasons other than forgetting. Thinking over the past 2 weeks, were there any days when you did not take your medicine?		
Have you ever cut back or stopped taking your medicine without telling your doctor because you felt worse when you took it?		
When you travel or leave home, do you sometimes forget to bring along your medicine?		
Did you take all your medicines yesterday?		
When you feel like your symptoms are under control, do you sometimes stop taking your medicine?		
Taking medicine every day is a real inconvenience for some people. Do you ever feel hassled about sticking to your treatment plan?		
How often do you have difficulty remembering to take all your medicine?		A = 0; B-E = 1

__ A. Never/rarely
__ B. Once in a while
__ C. Sometimes
__ D. Usually
__ E. All the time

LOW ADHERENCE (SCORE>2)

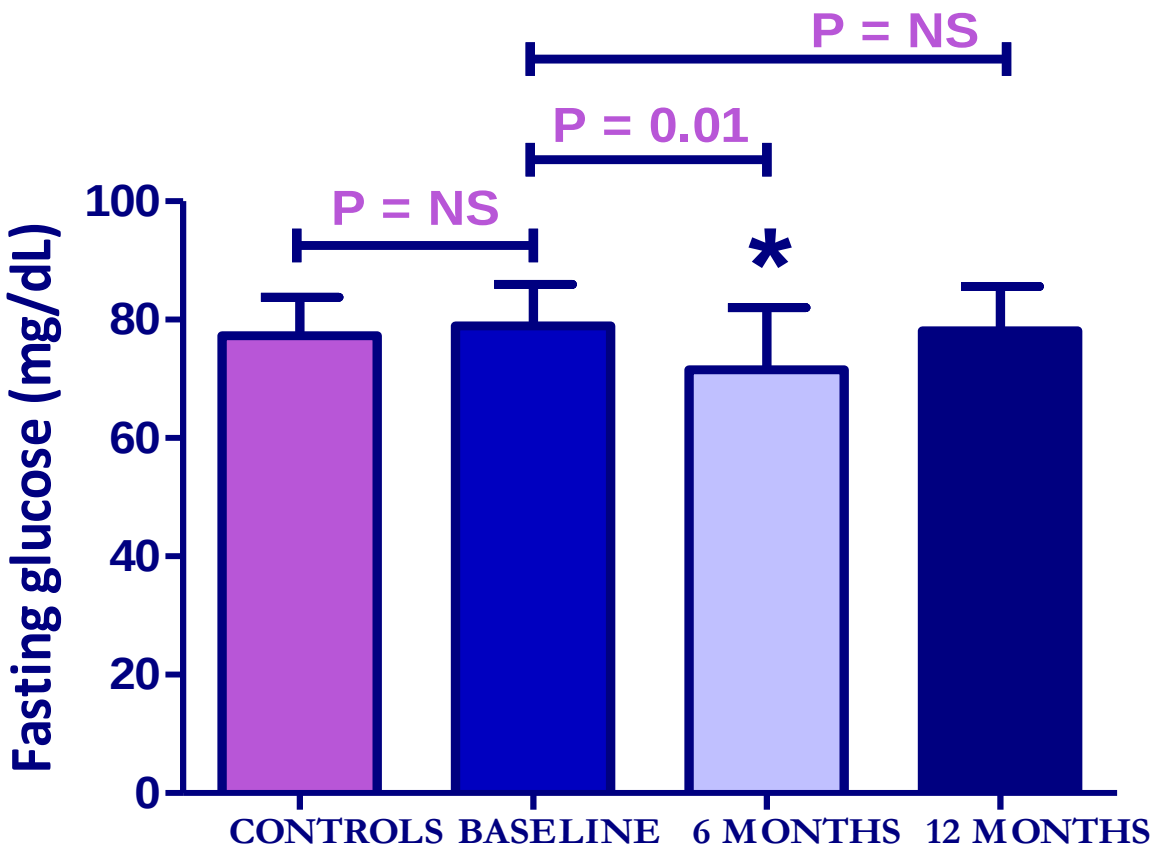
MEDIUM ADHERENCE (SCORE 1-2)

HIGH ADHERENCE (SCORE 0)

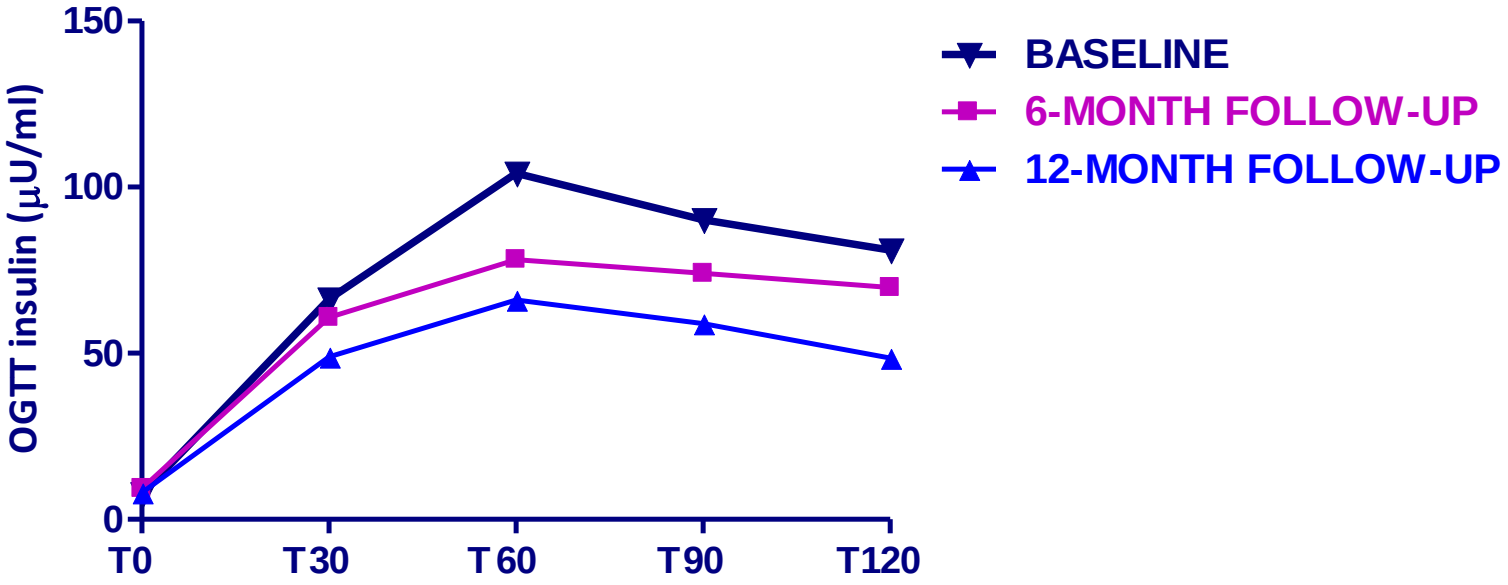
Morisky DE. et al Concurrent and predictive validity of a self-reported measure of medication adherence *Med Care* 1986; 24: 67-74

RESULTS

GLUCOSE PROFILE

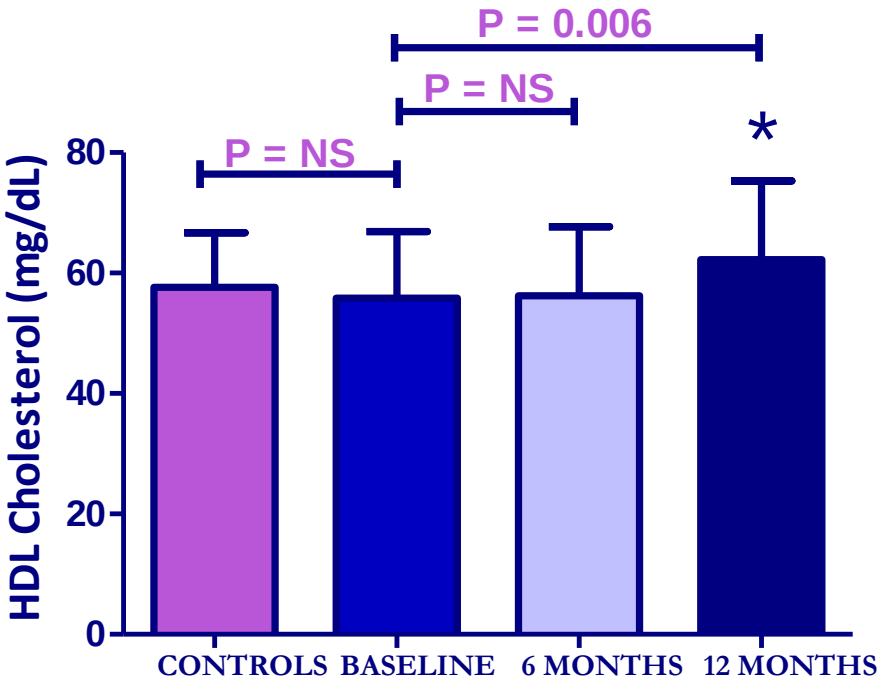


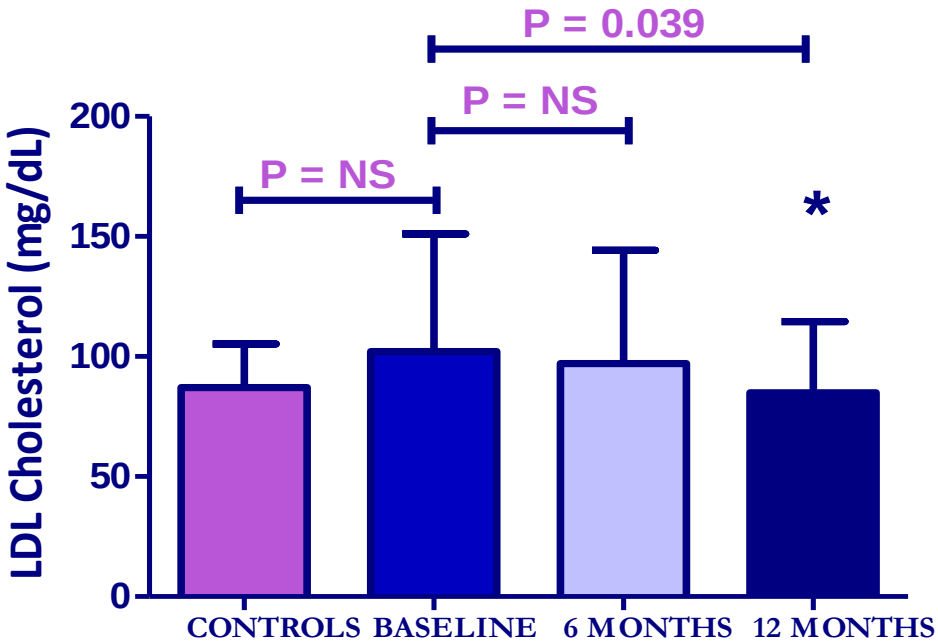
OGTT: INSULIN



BASELINE	6 MONTH FOLLOW-UP	12 MONTH FOLLOW-UP
MS+Diabetes mellitus (1 pt)	IGT	Normal glucose profile
IGT (1pt)	Normal glucose profile	Normal glucose profile

LIPID PROFILE





HORMONAL PROFILE 1

ALL PATIENTS

PARAMETERS	CONTROLS	BASELINE	6 MONTHS	P (0-6)	12 MONTHS	P (0-12)	P (6-12)
ACTH (pg/mL)	28.1 ± 24.63	95.5 ± 162 *	44.2 ± 47.6	NS	48.8 ± 57	NS	NS
Cortisol (ng/L)	152.3 ± 85.1	135.4 ± 105 *	197 ± 76.4	0.014	189.55± 39.8	0.042	NS
UFC (µg/24h)	144.1 ± 103.8	126.1 ± 68.1 *	186.3 ± 149.7	NS	143.6 ± 85.7	NS	NS

EXCLUDING 2 PTS TREATED WITH PREDNISONE AT BASELINE

PARAMETERS	CONTROLS	BASELINE	6 MONTHS	P (0-6)	12 MONTHS	P (0-12)	P (6-12)
ACTH (pg/mL)	28.1 ± 24.5	102.8 ± 170.6 *	37.4 ± 46	NS	38.9 ± 43.4	NS	NS
Cortisol (ng/L)	153.2 ± 88.2	149.4 ± 103 *	209.2 ± 71.9	0.039	189.3± 42.4	NS	NS
UFC (µg/24h)	133.7 ± 109.7	137.3 ± 63.4 *	191.7 ± 158	NS	135.1 ± 80.4	NS	NS

* ***NS*** *baseline vs controls*

HORMONAL PROFILE 2

ALL PATIENTS

PARAMETERS	CONTROLS	BASELINE	6 MONTHS	P (0-6)	12 MONTHS	P (0-12)	P (6-12)
Aldosterone (pg/ml)	86.6 ± 67.8	132.2 ± 144.7 *	118.6 ± 153.6	NS	118.7 ± 162.5	NS	NS
Renin (pg/ml)	19.3 ± 12.3	27.4 ± 34.6 *	13.5 ± 20.7	0.004	25.6 ± 31.3	NS	0.012

EVALUATION ON 11 PTS WITH CLASSIC FORM: SALT WASTING

PARAMETERS	CONTROLS	BASELINE	6 MONTHS	P (0-6)	12 MONTHS	P (0-12)	P (6-12)
Aldosterone (pg/ml)	45.4 ± 29.5	122.7 ± 184.3 *	80.9 ± 75.7	NS	121.3 ± 212	NS	NS
Renin (pg/ml)	21.6 ± 14.5	24.5 ± 37.8 *	13.3 ± 27.5	0.02	30.7 ± 40.8	NS	0.027

* ***NS*** *baseline vs controls*

HORMONAL PROFILE 3

MALES

PARAMETERS	CONTROLS	BASELINE	6 MONTHS	P (0-6)	12 MONTHS	P (0-12)	P (6-12)
17 OHP (ng/ml)	28.1 ± 53.3	16.7 ± 14.2 *	28.3 ± 25.6	NS	42 ± 72.7	NS	NS
Testosterone (ng/dl)	369.7 ± 238.2	431 ± 105.2 *	383.5 ± 204.6	NS	529 ± 82.6	NS	NS
DHEA-S (µg/dL)	110 ± 46.6	120.5 ± 76.1 *	86.7 ± 36.7	NS	115.2 ± 68.2	NS	NS
Δ-4 A (ng/mL)	2.2 ± 1.3	4.6 ± 3.9 *	5.6 ± 2.9	NS	4.5 ± 3.8	NS	NS

FEMALES

PARAMETERS	CONTROLS	BASELINE	6 MONTHS	P (0-6)	12 MONTHS	P (0-12)	P (6-12)
17 OHP (ng/ml)	10.6 ± 13.5	19.9 ± 39.1 *	18.2 ± 21.1	NS	17.9 ± 18	NS	NS
Testosterone (ng/dl)	51.4 ± 42.9	42.6 ± 33.3 *	89.5 ± 106.6	NS	56.6 ± 24.7	NS	NS
DHEA-S (µg/dL)	141.2 ± 182	114.2 ± 107.7 *	97.1 ± 93.3	NS	148.8 ± 132.4	NS	0.021
Δ-4 A (ng/mL)	2.8 ± 2.6	3.3 ± 2.6 *	4.1 ± 3.2	NS	4.5 ± 1.5	NS	NS

* ***NS*** *baseline vs controls*

Testosterone (n.v. 20-120 ng/dL) ; DHEA-S (n.v. 35-430 µg/dL); Δ-4 A (n.v. 1-4.5) (ng/mL)

QUALITY OF LIFE

4/18 pts (22%) IMPROVED VITALITY

4/18 pts (22%) IMPROVED WORKING ABILITY

7/18 pts (39%) IMPROVED PAIN PERCEPTION

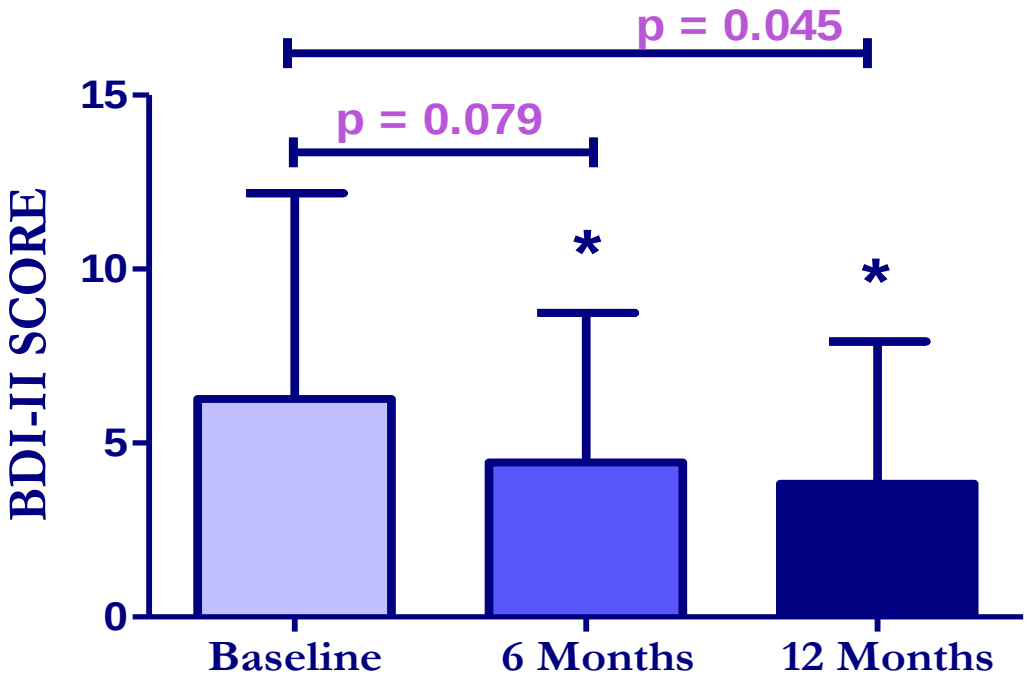
3/18 pts (17%) IMPROVED HEALTH PERCEPTION

3/18 pts (17%) IMPROVED SLEEP QUALITY

Øksnes M. et al Quality of life in European patients with Addison's disease: validity of the disease-specific questionnaire AddiQol *JCEM* 2012; 97(2):568-76

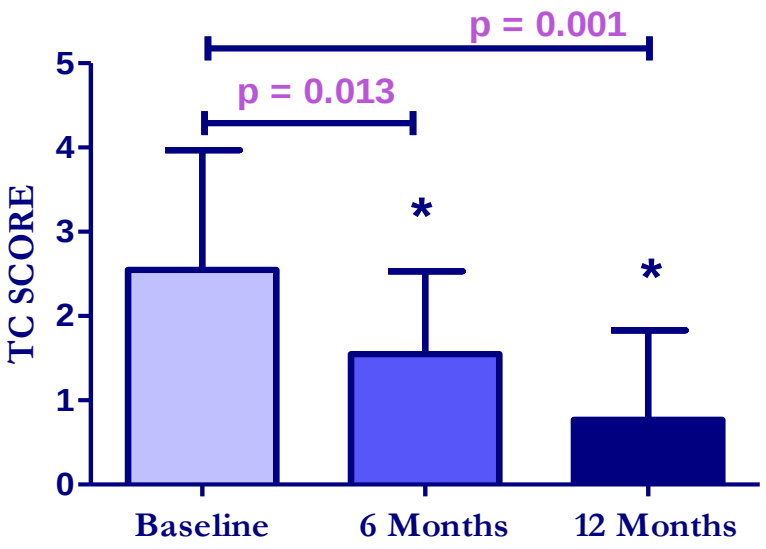
DEPRESSION STATUS

MINIMAL DEPRESSION (SCORE 0-13)
MILD DEPRESSION (SCORE 14-19)
MODERATE DEPRESSION (SCORE 20-28)
SEVERE DEPRESSION (SCORE 29-63)



Beck AT, et al. Journal of Personality Assessment 1996; 67: 588–97

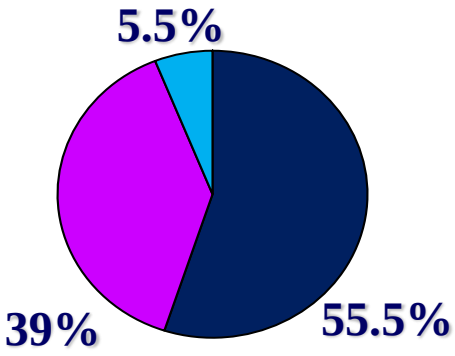
TREATMENT COMPLIANCE



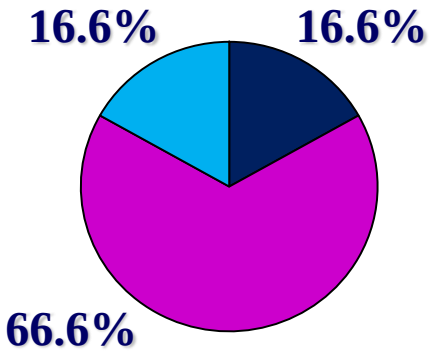
LOW ADHERENCE (SCORE>2)

MEDIUM ADHERENCE (SCORE 1-2)

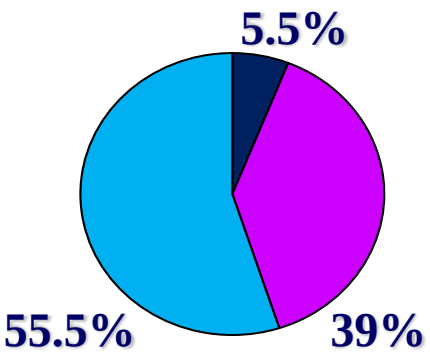
HIGH ADHERENCE (SCORE 0)



BASELINE



6 MONTHS



12 MONTHS

Morisky DE, et al . *Med Care* 1986; 24: 67-74

SAFETY AND TOLERABILITY PROFILE

- DR-HC was generally safely conducted and well tolerated
- After 1 month of treatment 2/18 patients complained asthenia requiring a 5 mg drug dose increase
- During the following months other 4/18 pts required a 5 mg increase on the basis of clinical and hormonal evaluation
- No changes were required in fludrocortisone dose in SW patients

FEMALES

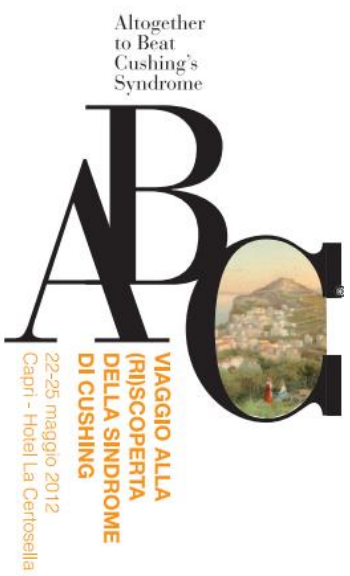
- No clinical worsening associated with hyperandrogenism was observed
- 4/14 females reported only once in the first 3 months of treatment menstrual cycle abnormalities
- 3 of these 4 pts, after 3 months of treatment, showed, associated with menstrual cycle abnormalities, androgen levels higher than normal, requiring a 5 mg drug dose increase
- After 6 and 12 months no pts showed neither androgen levels higher than normal nor menstrual cycle abnormalities

CONCLUSIONS

The switch from conventional GCs to DR-HC:

- Improves **glucose** and **lipid metabolism**
- Improves **depression status** and **compliance to treatment**
- Maintains a **good hormone control**
- Ensures a **good safety profile**, with reported adverse events similar to those commonly observed during conventional GCs

T H A N K S


Altogether
to Beat
Cushing's
Syndrome
ABC
VIAGGIO ALLA
(RI)SCOPERTA
DELLA SINDROME
DI CUSHING
22-25 maggio 2012
Capri - Hotel La Certosella


Altogether
to Beat
Cushing's
Syndrome
ABC
VIAGGIO ALLA
(RI)SCOPERTA
DELLA SINDROME
DI CUSHING
seconda edizione
Capri \ 15-18 maggio 2013
Certosa di San Giacomo
Hotel della Piccola Marina


Altogether
to Beat
Cushing's
Syndrome
ABC
Viaggio alla
(ri)scoperta
della Sindrome
di Cushing
Terza Edizione
Sorrento, 27-30 maggio 2014


Altogether
to Beat
Cushing's
Syndrome
ABC
Viaggio alla
(ri)scoperta
della Sindrome
di Cushing
Quarta Edizione
Napoli, 5-7 maggio 2015
Hotel S. Lucia

DOSE ADJUSTEMENT

- **DOSE ESCALATION:** after **ONE month** dose was eventually increased based on:
  - Clinical evaluation: presence of moderate/severe signs and symptoms of hypocortisolism as fatigue, vomiting, nausea, hypotension (SBP< 100 mmHg)
- **DOSE ESCALATION:** after **THREE months** dose was eventually increased based on:
  - Clinical evaluation: presence of moderate/severe signs and symptoms of hypocortisolism as fatigue, vomiting, nausea
  - Blood pressure: hypotension (SBP<100 mmHg)
  - Biochemical evaluation:
    - Na < 135 mmol/L
    - K > 5 mmol/L
    - hypoglycemia(< 60 mg/dL)
  - Hormonal evaluation: at least 1 of these 3 criteria:
    - Morning serum cortisol levels < 50 ng/mL
    - A4 androstenedione levels ≥ 5 ng/ml (in any menstrual cycle phase)
    - Testosterone levels in females > 120 ng/dl
    - In presence of normal androgens dose was also increased in case of:
    - 17OH progesterone > 50 ng/mL