

Terapia dell' insufficienza surrenalica: verso una migliore qualità di vita



Terapia sostitutiva: dove siamo oggi?

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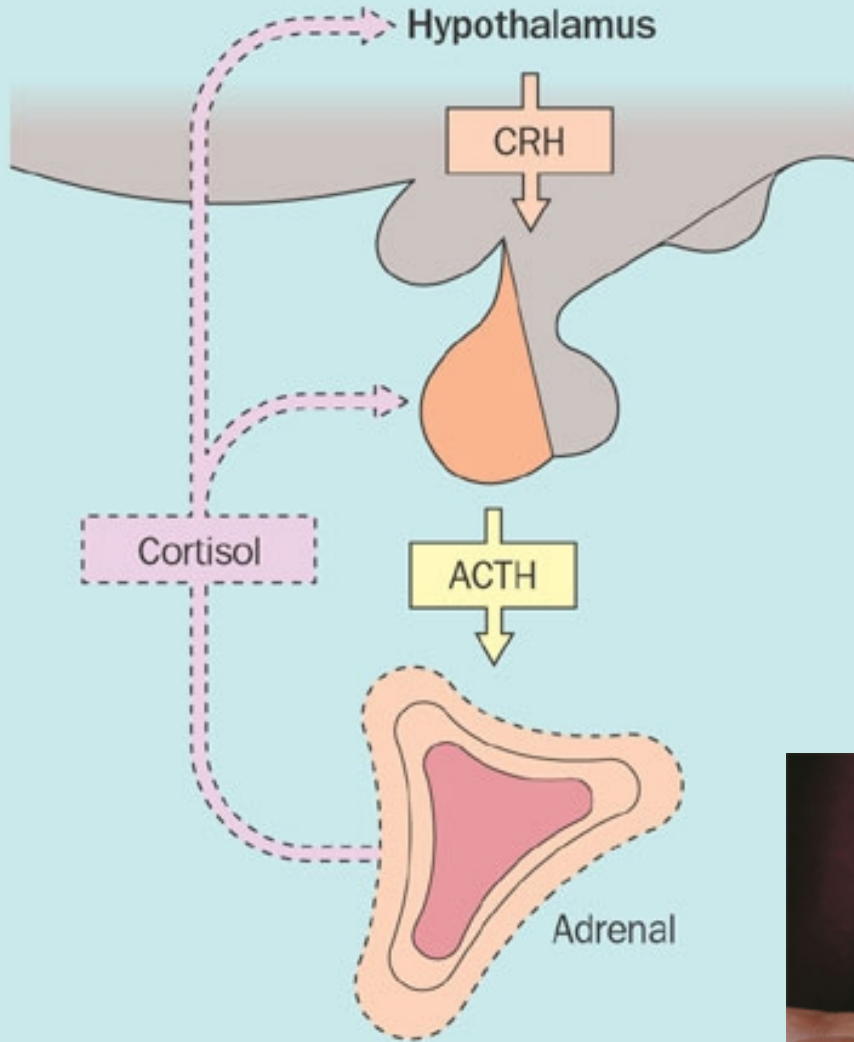
Terapia sostitutiva: la storia



Roma,
9-11 novembre 2012

- **1937**: viene sintetizzato **11-DOC**
- **1948**: vengono sintetizzati **cortisone** ed **idrocortisone**
- **1948**: **prima pubblicazione** su efficacia del **cortisone** nel trattamento dell'**artrite reumatoide**
- **1950**
 - **Premio Nobel** Medicina a Philip Hench, Edward Kendall e Tadeus Reichstein per **cortisone** ed **idrocortisone**
 - George Widmer Thorn e PH Forsham per primi usano il **cortisone acetate nella malattia di Addison**
 - Merck rende disponibile il **cortisone** negli USA
 - Viene sintetizzato **fludrocortisone**

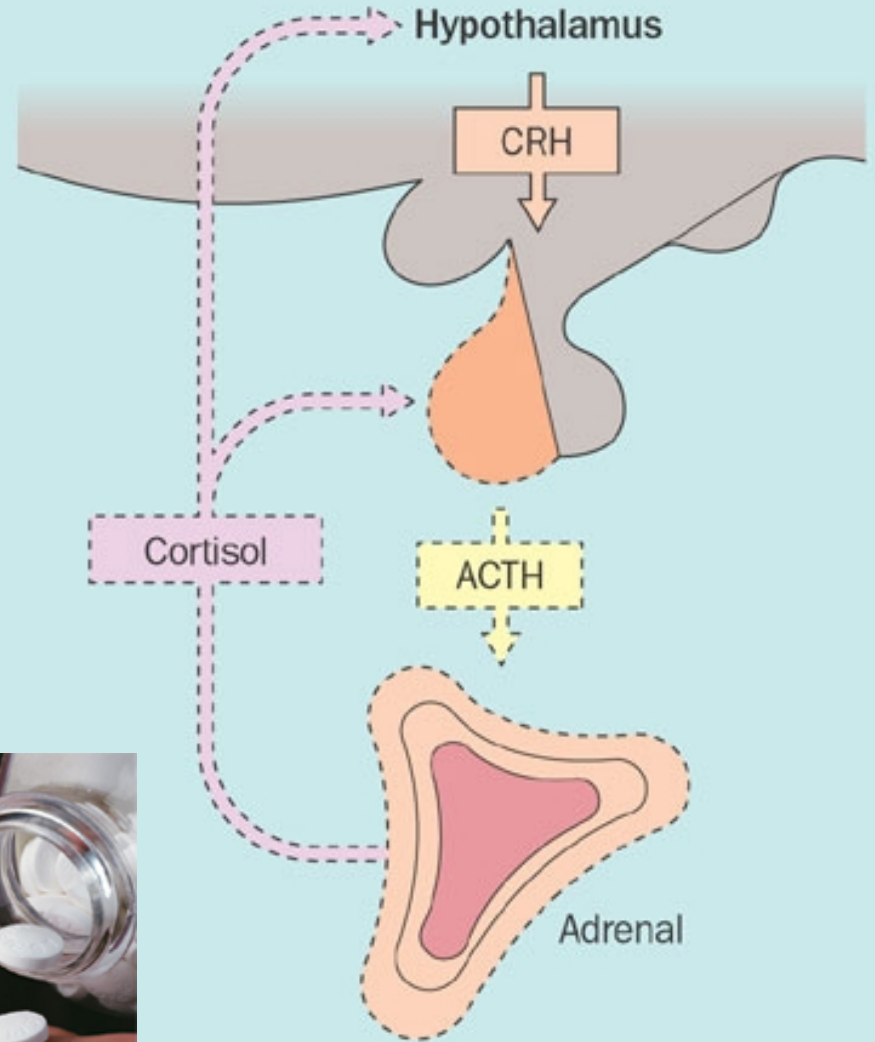
Primary adrenocortical insufficiency



GC

MC

Secondary adrenocortical insufficiency



GC

DHEA ?





Terapia sostitutiva GC



Roma,
9-11 novembre 2012

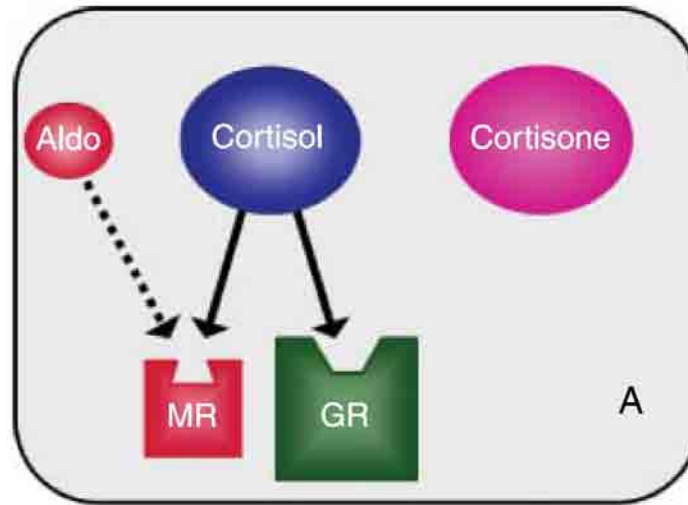
Opzioni terapeutiche

1. Cortisone acetato
2. Idrocortisone
3. Altri steroidi

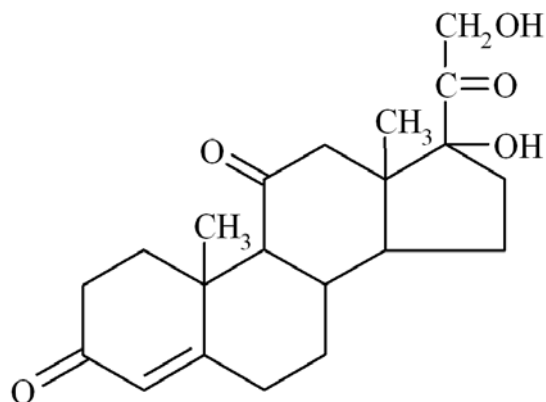
Tipologia di trattamento

1. Dose
2. Modalità di somministrazione

Opzioni terapeutiche



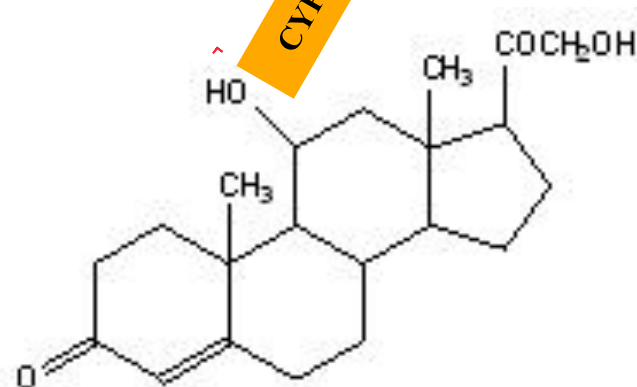
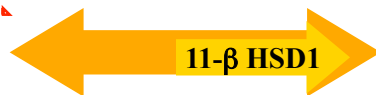
Steroide	Dose equivalente (mg)	Potenza relativa anti-infiammatoria	Potenza relativa mineralcorticoidea	Emivita plasmatica (h)	Emivita biologica (h)
Cortisone acetato	25	0.8	2	0.5	8-12
Idrocortisone	20	1	2	1.5-2	8-12
Metilprednisolone	4	5	0	1.5-3	18-36
Prednisone	5	4	1	1	18-36
Prednisolone	5	4	1	2-3.5	18-36
Triamcinolone	4	5	0	3.5-4	18-36
Betametasone	0.6-0.75	20-30	0	5.5	36-54
Desametasone	0.75	20-30	0	2-3.5	36-54



CORTISONE

5 β --reduttasi

**Tetraidrocortisone
(THE)**



CORTISOLO.

5 β --reduttasi

5 β - diidrocortisolo

**5 β -
tetraidrocortisolo
(THF)**

5 α --reduttasi

5 α - diidrocortisolo

**5 β -
tetraidrocortisolo
(allo-THF)**

6 β -OHcortisolo

Comparison of Absorption of Cortisone Acetate and Hydrocortisone Hemisuccinate*

BRUCE L. FARISS,† SATOSHI HANE, JEANETTE SHINSAKO, AND PETER H. FORSHAM

When cortisone acetate and hydrocortisone were given by **mouth** to three of the four patients in this study, **the response to each agent was similar**. Therefore, for those patients requiring chronic glucocorticoid therapy, **oral administration of cortisone acetate is sufficient and appropriate**.

TABLE 2 and ACT		Steroids									
Steroid		4 h									
Cortisone acetate		49									
Mean ± SEM		24									
Hydrocortisone hemisuccinate		12									
HD		28 ± 11									
HH		30									
Mean ± SEM		10									
	HD	8.1	34.5	40.8	29.8	20.7	192	144	45	16	10
	HH	5.9	85.5	64.8	54.5	41.9	120	68	26	13	15
	Mean ± SEM	10.1 ± 3.2	78.5 ± 15.5	64.5 ± 11.3	48.4 ± 9.7	36.4 ± 8.0	275 ± 123	168 ± 66	42 ± 9	26 ± 11	18 ± 6

* Each steroid was given as a single 50-mg oral dose, and blood samples were collected at 0, 1, 2, 3, and 4 h.

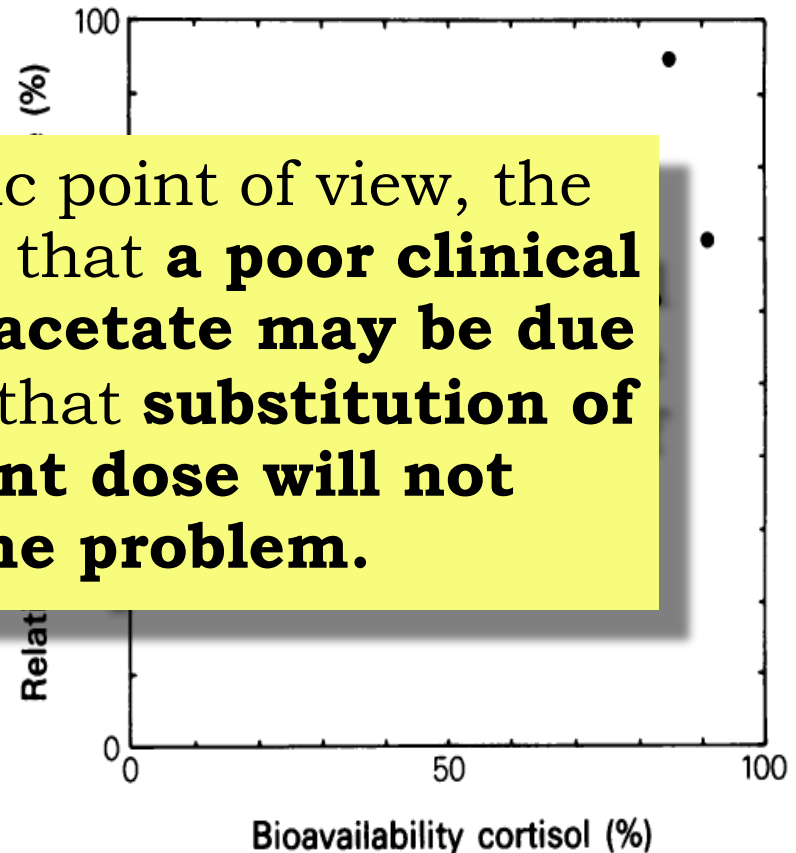
Plasma cortisol delivery from oral cortisol and cortisone acetate: relative bioavailability

V. J. HEAZELWOOD¹, J. P. GALLIGAN¹, G. R. CANNELL¹, F. BOCHNER^{2*} & R. H. MORTIMER¹

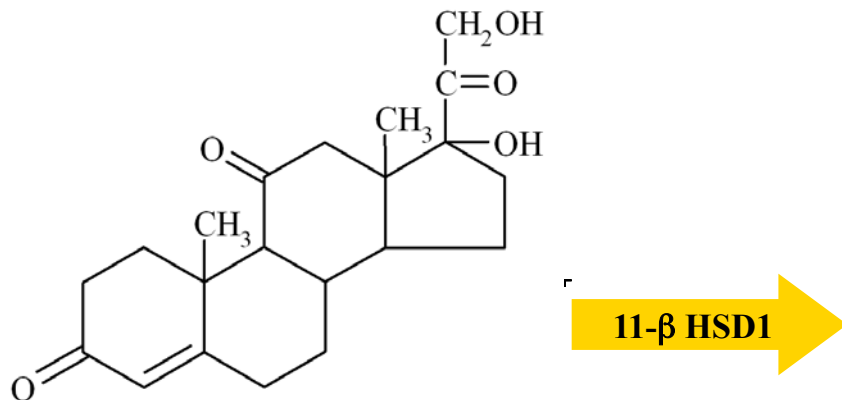
Table 4 AUC and bioavailability

Number	AUC (nmol l ⁻¹ h)		Bioavailability (%)		
	Oral cortisol	Oral cortisone acetate	Oral cortisol	Oral cortisone acetate*	
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					
11	12333	10204	6806	82.7	61.8
12	7196	2488	2069	34.6	32.2
Mean	11795	5790	4109	54.4	43.7
s.e. mean	1507	691	526	6.9	6.6

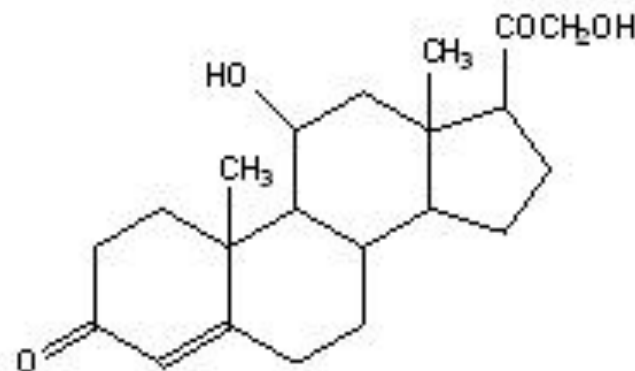
From the clinical therapeutic point of view, the results of this study indicate that **a poor clinical response to oral cortisone acetate may be due to poor bioavailability** and that **substitution of oral cortisol in equivalent dose will not adequately solve the problem.**



* Relative bioavailability of cortisone was calculated as described in the methods section.



CORTISONE



CORTISOLO



■ **Deficit congenito**

■ **Epatopatie avanzate**

■ **Farmaci:**

rhGH

PPARα agonisti (fibrati)

PPARγ agonisti e LXRα

agonisti

Flavonone

Carbenoxolone

Ac. glicirizzico

Ac. chenodesossicolico

■ Bassa clearance metabolica
 ■ Basso volume distribuzione
 ■ Assorbimento intest. > 90%
 ■ Biodisponibilità 96%

■ T_{max} 1.2-1.5 h

■ C_{max} 550-650 nM

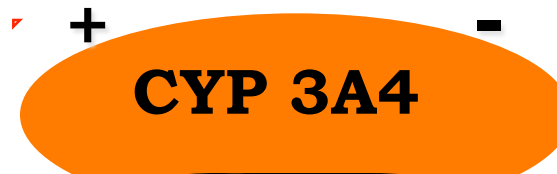
rifampicina

itraconazolo

carbamazepina

ritonavir

fenitoina



nefazodone

fenobarbital

claritromicina

mitotane

CORTISOLO

6β-OHcortisolo



Terapia sostitutiva GC



Roma,
9-11 novembre 2012

Tipologia di trattamento

1. Dose
2. Modalità di somministrazione



TREATMENT OF ADRENAL CORTICAL INSUFFICIENCY

BY

J. D. N. NABARRO, M.D., F.R.C.P.

AND

G. WALKER, M.B., M.R.C.P.*The Institute of Clinical Research, the Middlesex
Hospital, London*

Practical Experience

Hydrocortisone production in a normal subject may be assessed by studies with isotope-labelled steroid (Peterson and Wyngaarden, 1955), or by measurement of urinary glucocorticoid excretion (Moxham and Nabarro, 1956). The adrenal glands of a normal adult secrete 20–25 mg. of hydrocortisone a day, which is equivalent to about 25–37.5 mg. of cortisone acetate. Patients who have had total adrenalectomy and those with severe Addison's disease can usually

The adrenal glands of a normal adult secrete **20-25 mg of hydrocortisone a day**, which is **equivalent to about 25-37.5 mg of cortisone acetate**. Patients who have had total adrenalectomy and those with severe Addison's disease can usually be maintained **on 37.5 mg of cortisone a day**. Because of its rapid absorption and conjugation after oral administration, cortisone should be given as evenly spaced doses of 12.5 mg.

Daily Cortisol Production Rate in Man Determined by Stable Isotope Dilution/Mass Spectrometry

NORA V. ESTEBAN, THÉRÈSE LOUGHLIN, ALFRED L. YERGEY,
JOANNA K. ZAWADZKI, JOHN D. BOOTH, JORG C. WINTERER, AND
D. LYNN LORIAUX



**5-10 mg/m² BSA
= 10-20 mg/m² HC os**

Steroids

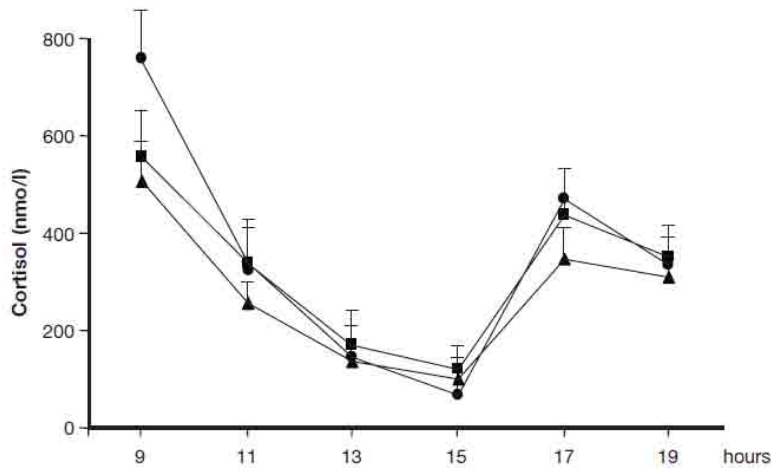
Cortisol production rate measurement by stable isotope dilution using gas chromatography-negative ion chemical ionization mass spectrometry¹

David D. Brandon^{a,*}, Lorne M. Isabelle^b, Mary H. Samuels^a, John W. Kendall^a,
D. Lynn Loriaux^a

Comparison of different regimens of glucocorticoid replacement therapy in patients with hypoadrenalism

L. Barbetta¹, C. Dall'Asta¹, T. Re², R. Libè³, E. Costa⁴, and B. Ambrosi¹

J. Endocrinol. Invest. 28: 632-637, 2005



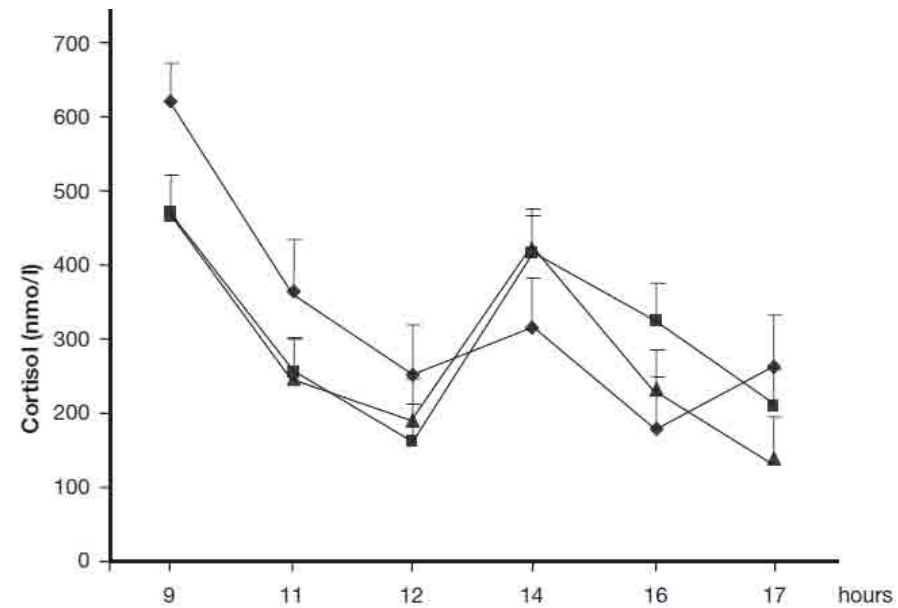
twice daily
(25 mg h 7
12.5 mg h 15)

thrice daily

B (rhombus): 25 mg h 7, 6.25 mg h 12, 6.25 mg h 17

C (square): 12.5 mg h 7, 12.5 mg h 12, 12.5 mg h 17

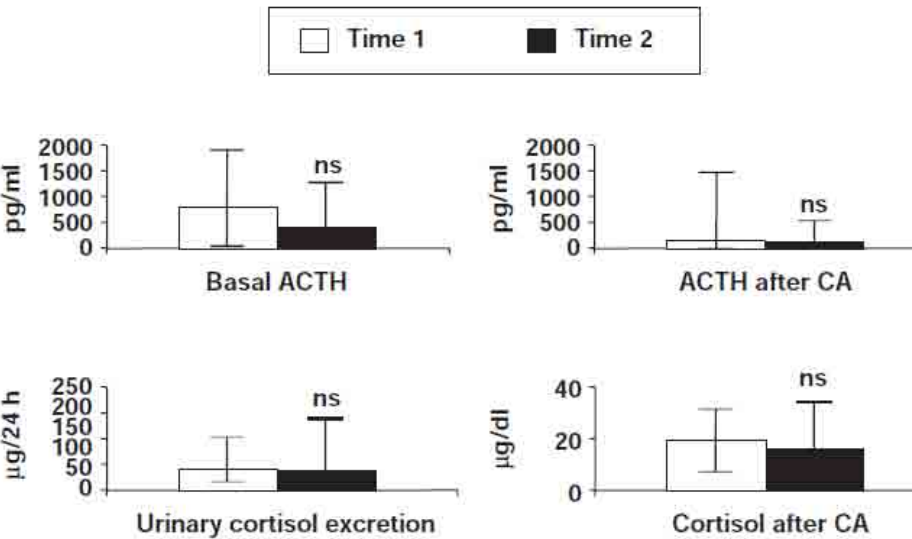
D (triangle): 12.5 mg h 7, 6.25 mg h 12, 6.25 mg h 17



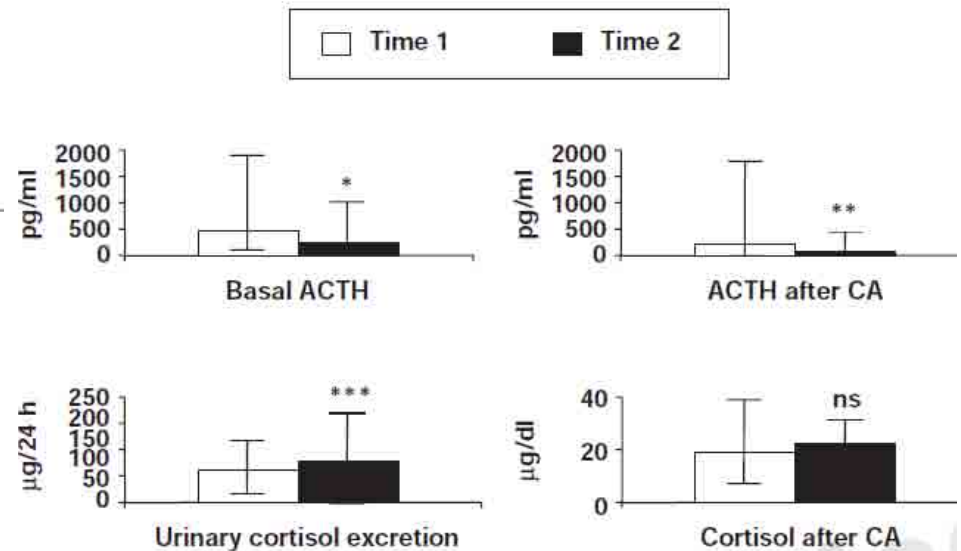
Improvement of treatment of primary adrenal insufficiency by administration of cortisone acetate in three daily doses

S. Laureti, A. Falorni and F. Santeusanio

(*J. Endocrinol. Invest.* 26: 1071-1075, 2003)



thrice daily
(16 pts; 37.5-50 mg/day)



twice daily
(18 pts; 25-50 mg/day)

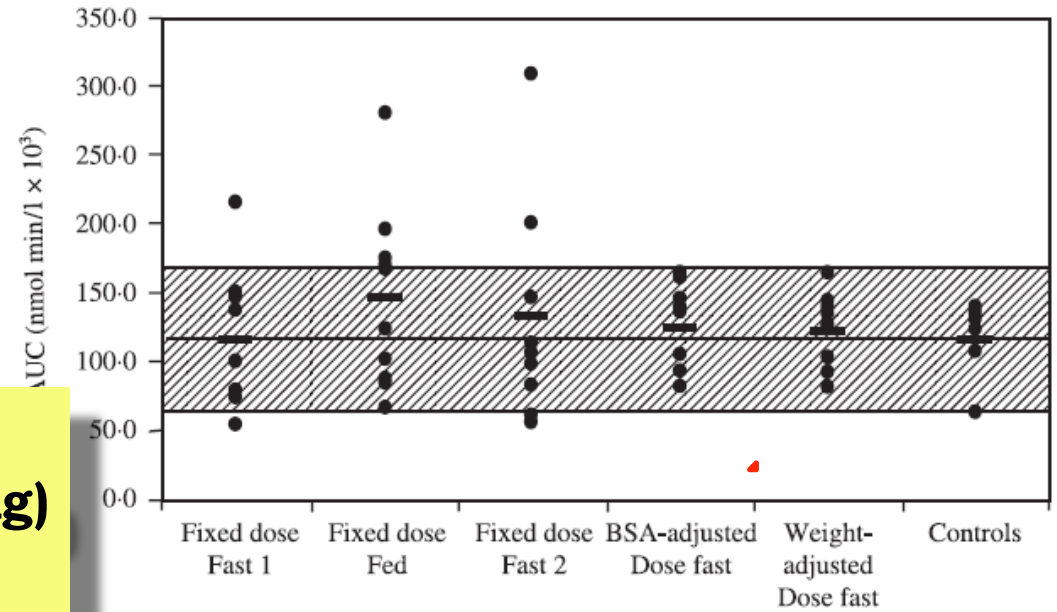
Weight-related dosing, timing and monitoring hydrocortisone replacement therapy in patients with adrenal insufficiency

Clinical Endocrinology (2004) 61, 367–375

Peak M. Mah*‡, Richard C. Jenkins*‡,
Amin Rostami-Hodjegan†‡, John Newell-Pri
Anita Doane*, Victoria Ibbotson*, Geoffrey T.
and Richard J. Ross*

*Divisions of Clinical Sciences (North) and †Acad
of Molecular Pharmacology and Pharmacogen
University of Sheffield, UK

**Weight-adjusted (0.12 mg/kg)
Thrice daily
Before food**



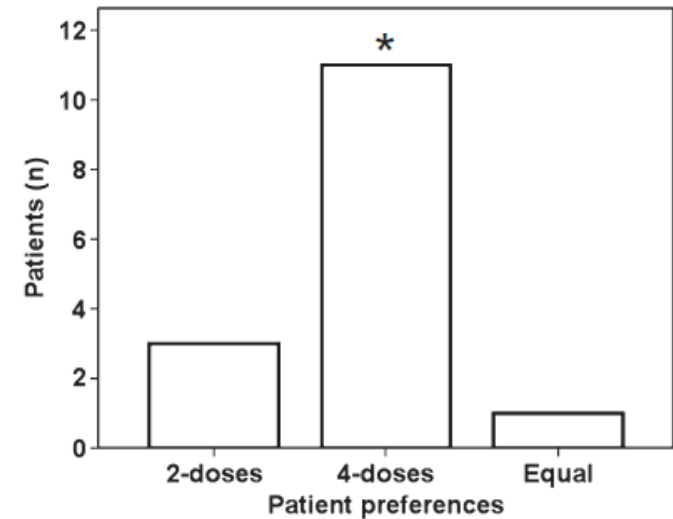
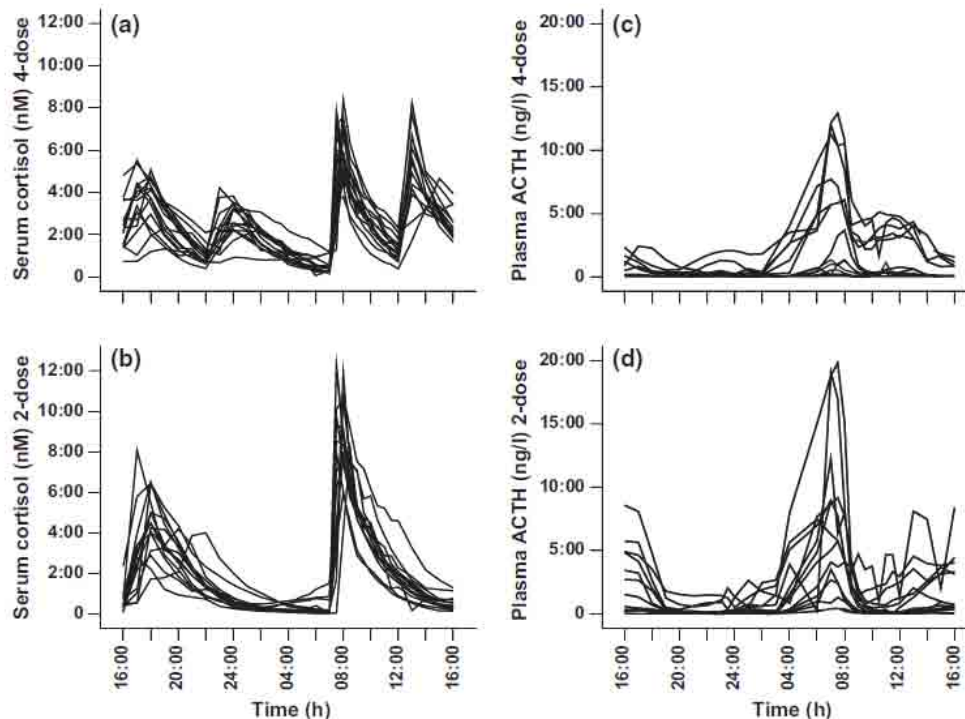
Hydrocortisone, Merck Sharp & Dohme) and dividing tablets into 2.5 mg quanta

Patient weight (kg)	Total dose per day (mg)	First morning dose (mg)	Second midday dose (mg)	Third evening dose (mg)
50–54	10.0	5.0	2.5	2.5
55–74	15.0	7.5	5.0	2.5
75–84	17.5	10.0	5.0	2.5
85–94	20.0	10.0	7.5	2.5
95–114	22.5	12.5	7.5	2.5
115–120	25.0	15.0	7.5	2.5

A randomized, double-blind, crossover study comparing two- and four-dose hydrocortisone regimen with regard to quality of life, cortisol and ACTH profiles in patients with primary adrenal insufficiency

Bertil Ekman*, Margareta Bachrach-Lindström†, Torbjörn Lindström*, Jeanette Wahlberg*, Johan Blomgren‡ and Hans J. Arnqvist§

Clinical Endocrinology (2012) 77, 18–25



Four times daily

10 mg at 07:00, 10 mg at 12:00,
5 mg at 16:00, 5 mg at 22:00



Monitoraggio della terapia GC



Roma,
9-11 novembre 2012

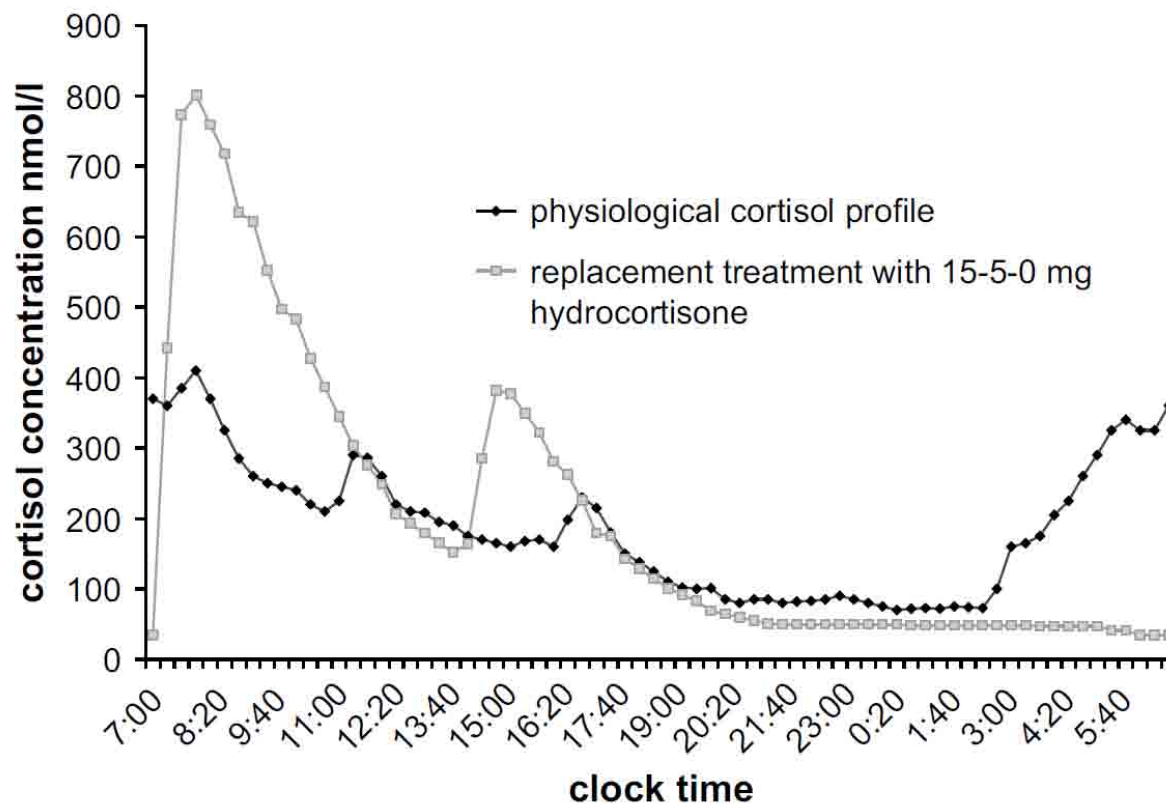
Valutazioni ematochimiche

- 1. Cortisolemia**
- 2. Cortisolo salivare**
3. ACTH
4. UFC

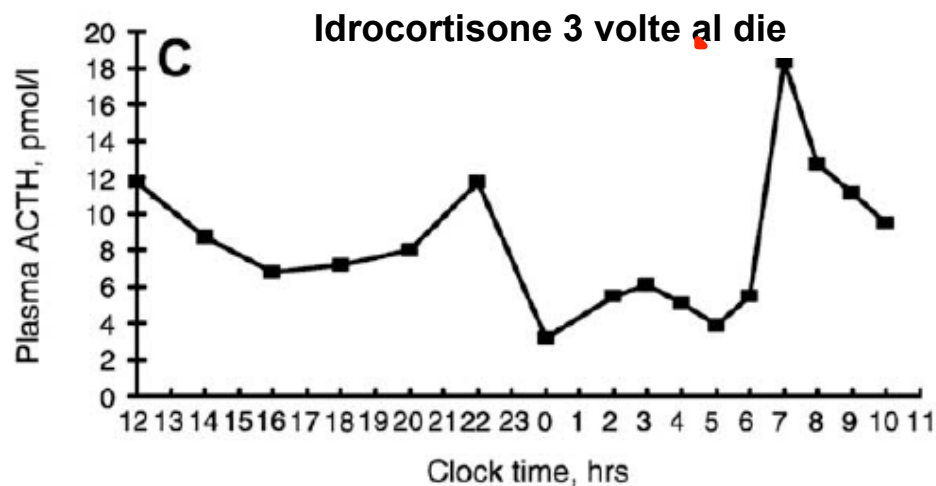
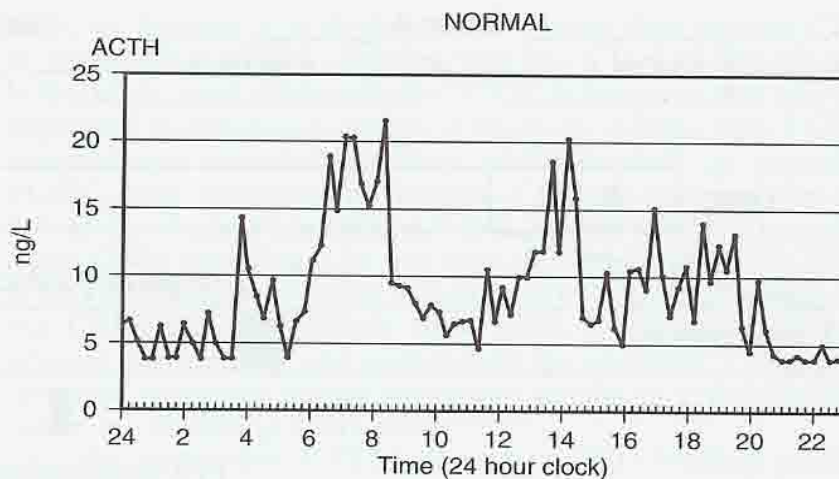
Valutazione clinica

- 1. Ricerca di segni e sintomi di sotto/sovra-dosaggio**
- 2. Valutazione della QoL**

... la terapia convenzionale **non** è in grado di mimare il **ritmo circadiano del cortisolo** essendo caratterizzata da un **picco sovra-fisiologico** dopo l'assunzione e livelli bassissimi alla sera...

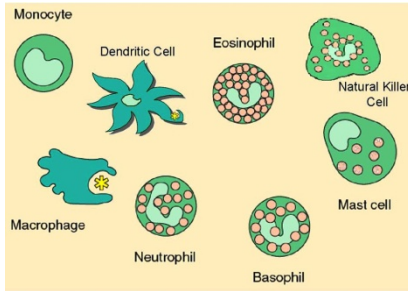


... **nell'ipocorticosurrenalismo primario** la terapia convenzionale **non** è in grado di ridurre i **livelli circolanti di ACTH** ...



GC: numerosi effetti

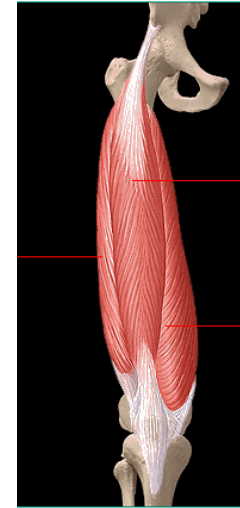
Sistema
immunitario



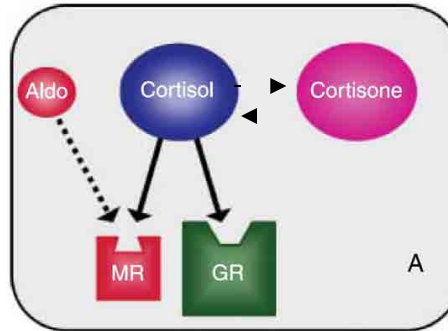
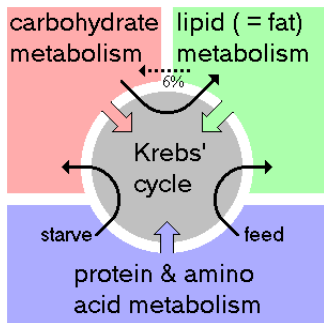
Sonno
Psiche



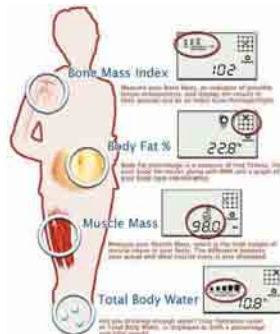
Muscolo



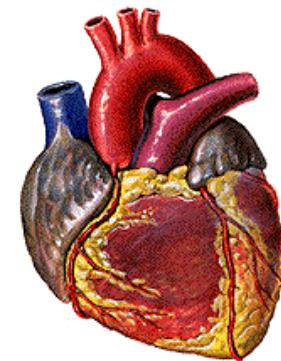
Bilancio
energetico



Composizione
corporea



Osso



Sistema
cardiovascolare

Premature Mortality in Patients with Addison's Disease: A Population-Based Study

Ragnhildur Bergthorsdottir, Maria Leonsson-Zachrisson, Anders Odén, and Gudmundur Johannsson

(J Clin Endocrinol Metab 91: 4849–4853, 2006)

Increased death risk and altered cancer incidence pattern in patients with isolated or combined autoimmune primary adrenocortical insufficiency

Sophie Bensing*†, Lena Brandt‡, Farnoush Tabarojt, Olof Sjöberg§, Bo Nilsson§, Anders Ekbohm‡,
Paul Blomqvist‡ and Olle Kämpet

Clinical Endocrinology (2008) 69, 697–704

Normal overall mortality rate in Addison's disease, but young patients are at risk of premature death

Martina M Erichsen¹, Kristian Løvås^{1,2}, Kristian J Fougner³, Johan Svartberg^{4,5},
Erik R Hauge⁶, Jens Bollerslev^{7,8}, Jens P Berg^{8,9,10}, Bjarne Mella¹¹ and Eystein S Husebye^{1,2}

Metabolic and cardiovascular profile in patients with Addison's disease under conventional glucocorticoid replacement

R. Giordano¹, S. Marzotti², M. Balbo³, S. Romagnoli², E. Marinazzo³, R. Berardelli³, G. Migliaretti⁴, A. Benso³, A. Falorni², E. Ghigo³, and E. Arvat³

38 AD under conventional GC (HC 30 mg/day, CA 37.5 mg/day) compared with 38 age-, sex- and BMI-matched CS

	AD	CS	<i>p</i>
Age (yr)	50.2±2.2	50.4±2.3	ns
BMI (Kg/m ²)	24.6±0.4	24.4±0.4	ns
Waist (cm)	94.2±2.3	85.8±1.9	<0.05
ACTH (pg/ml)	486.8±61.6	23.0±1.6	<0.0005
PRA (ng/ml/h)	8.2±0.8	1.3±0.1	<0.0005
DHEAS (µg/dl)	18.6±2.2	97.0±6.2	<0.0005
Glucose (mg/dl)	79.3±1.3	81.9±1.3	ns
Insulin (mU/l)	9.8±1.1	9.3±0.4	ns
HOMA	1.9±0.2	1.9±0.1	ns
2h-Glucose (mg/dl)	107.7±4.8	95.3±2.4	ns
Total C (mg/dl)	205.0±6.7	193.9±3.9	ns
HDL C (mg/dl)	64.2±2.5	61.0±1.6	ns
LDL C (mg/dl)	117.5±5.2	112.6±3.5	ns
TG (mg/dl)	118.6±9.6	112.3±7.7	ns

... a higher prevalence of central adiposity, impaired glucose tolerance and dyslipidemia in AD ...

Table 1 Previous studies of bone mineral density in Addison's

Glucocorticoid replacement therapy and pharmacogenetics in Addison's disease: effects on bone

Kristian Løvås^{1,2}, Clara G Gjesdal^{3,4}, Monika Christensen⁵, Anette B Wolff^{1,6}, Bjørg Almås⁵, Johan Svartberg^{7,8}, Kristian J Fougner^{9,10}, Unni Syversen^{9,10}, Jens Bollerslev^{11,12}, Jan A Falch^{11,13}, Penelope J Hunt¹⁴, V Krishna K Chatterjee¹⁵ and Eystein S Husebye^{1,2}

(292 pts, HC 26.5 mg/day or CA 40.1 mg/day or Pred or DEX)... **BMD at the femoral neck and lumbar spine is reduced in Addison's disease ... not influenced by duration or type ... inverse association between GC dosage and BMD ...**

Bone Mineral Density Is Not Significantly Reduced in Adult Patients on Low-Dose Glucocorticoid Replacement Therapy

K. R. Koetz, M. Ventz, S. Diederich, and M. Quinkler

(J Clin Endocrinol Metab 97: 85–92, 2012)

(81 PAI and 41 CAH pts, HC 12.0±2.7 mg/m² and 15.5±7.8 mg/m²)... **BMD varied within the normal reference range in both cohorts ... lower Z-scores for femoral neck and Ward's region in CAH than in PAI...**

TABLE 2. Published mean scores in HRQoL studies applying the generic questionnaires SF-36 or GHQ in Addison's disease cohorts in Norway (15), United Kingdom (3, 5), and Germany (16, 25)

HRQoL domain	Scale	Score	Normative
General health	Vitality (SF-36)	47–52 ^a	58–60
	General health (SF-36)	56–59 ^a	71–77
	Self-esteem (GHQ)	8.1 ^b	7.6
	Coping (GHQ)	10.3	9.8
Physical health	Role-physical (SF-36)	46–66 ^a	78–87
	Physical functioning (SF-36)	PF 80–84	87–88
	Bodily pain (SF-36)	BP 76–79	75–79
Mental health	Role-emotional (SF-36)	57–75 ^a	82–86
	Social functioning (SF-36)	75–80	83–86
	Mental health (SF-36)	67–78	72–79
	Depression (GHQ)	7.2	7.3
	Anxiety (GHQ)	16 ^a	14

SF-36, Short Form-36; high scores are favorable. GHQ, General Health Questionnaire; low scores are favorable.

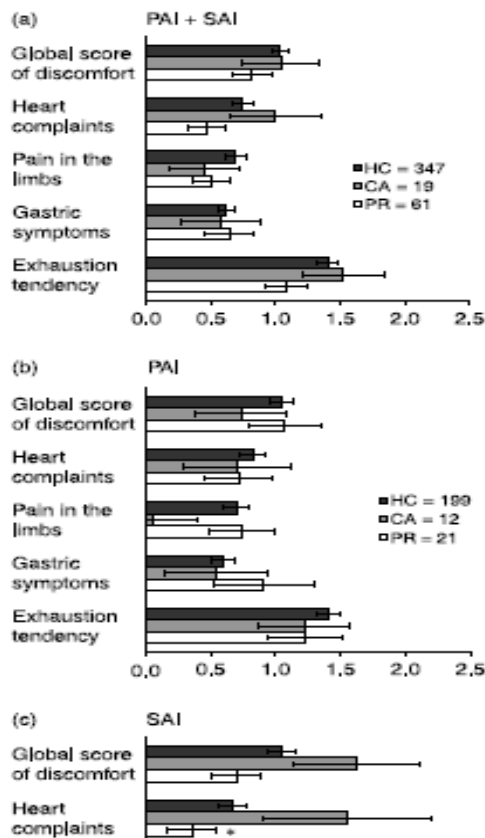
^a $P < 0.001$; ^b $P < 0.01$; differences from the normative data tested with Student *t* test (3, 5, 15) or Mann-Whitney *U* test (3, 5, 16, 25).

... Published studies of HRQoL in Addison's disease indicated reduced vitality and general health perception and limitation in physical and emotional functioning ...

CLINICAL STUDY

Impaired subjective health status in chronic adrenal insufficiency: impact of different glucocorticoid replacement regimens

Benjamin Bleicken*, Stefanie Hahnert^{1,*}, Melanie Loeffler¹, Manfred Ventz, Bruno Allolio¹ and Marcus Quinkler

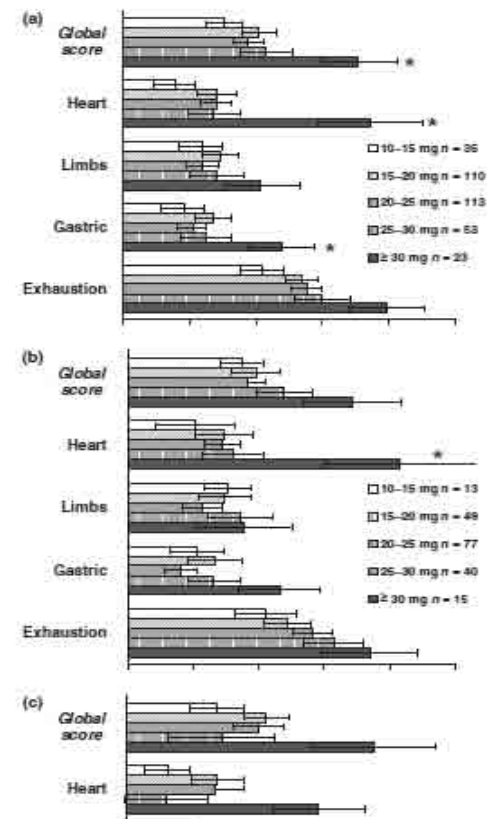


AI patients showed significantly impaired SHS compared with controls **irrespective of the glucocorticoid use for replacement.**

ORIGINAL ARTICLE

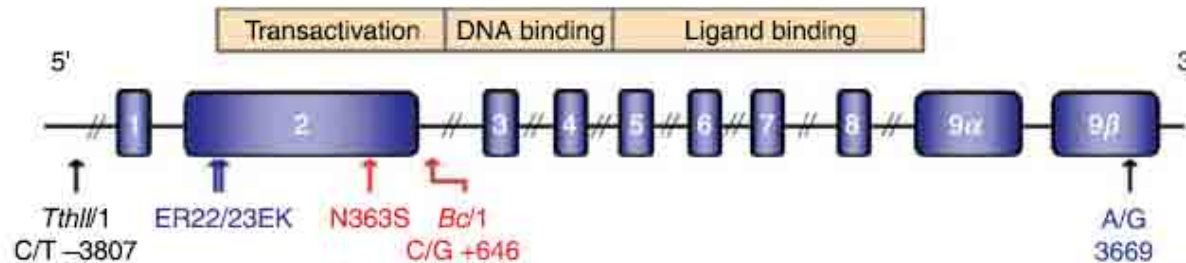
Influence of hydrocortisone dosage scheme on health-related quality of life in patients with adrenal insufficiency

Benjamin Bleicken^{***}, Stefanie Hahnert^{**}, Melanie Loeffler[†], Manfred Ventz^{*}, Oliver Deckert[‡], Bruno Allolio[†] and Marcus Quinkler^{*}



HC doses above 30 mg/day were associated with a worse health status. Thrice daily intake of HC was not superior to twice daily intake.

Differente sensibilità ai GC



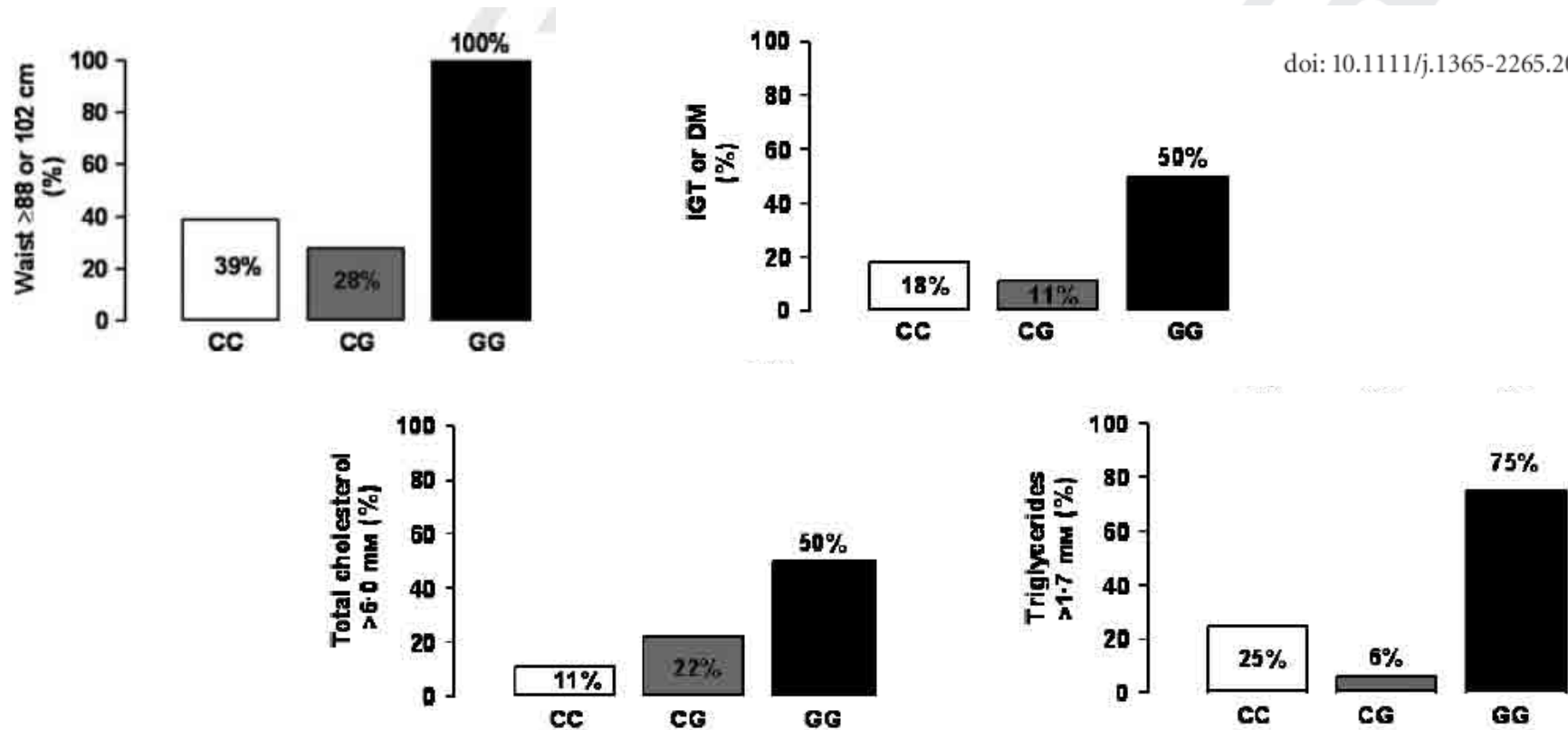
CR5

	ER22/23EK	N363S	<i>Bcl1</i> RFLP G allele
Allele frequency in population	~5%	~6%	~35%
<i>In vitro</i> glucocorticoid sensitivity		Enhanced sensitivity to Dex in PMN cell proliferation assay (161)	No effect on GR binding or number of PMN cells (36, 161)
<i>In vivo</i> glucocorticoid sensitivity	Resistance to Dex suppression (162)	Enhanced Dex suppression (161)	Enhanced Dex suppression (163); increased glucocorticoid-induced skin vasoconstriction (36); higher plasma cortisol (164)
Proposed molecular mechanism	Increased GR-A:GR-B transcript ratio (165)	?	?
Phenotype	Higher lean body mass (167); insulin sensitisation (162); protective lipid profile (162); lower CRP (168); reduced mortality (168); cognitive protection (169)	Obesity in some (161, 170–173) but not all (174, 175) cohorts; dyslipidaemia (116); coronary artery disease (116)	Inconsistent with obesity (36, 163, 164, 176–180); hyperinsulinaemia in obese (181); familial hypertension (182)

BCII polymorphism of the glucocorticoid receptor gene is associated with increased obesity, impaired glucose metabolism and dyslipidaemia in patients with addison's disease

Roberta Giordano*, Stefania Marzotti†, Rita Berardelli‡, Ioannis Karamouzis‡, Annalisa Brozzetti†, Valentina D'Angelo‡, Giulio Mengozzi§, Giorgia Mandrile*, Daniela Giachino*, Giuseppe Migliaretti¶, Vittorio Bini†, Alberto Falorni†, Ezio Ghigo‡ and Emanuela Arvat‡

doi: 10.1111/j.1365-2265.2012.04439.x





Terapia sostitutiva MC



Roma,
9-11 novembre 2012

Opzioni terapeutiche

1. Fludrocortisone

Tipologia di trattamento

1. Dose fissa

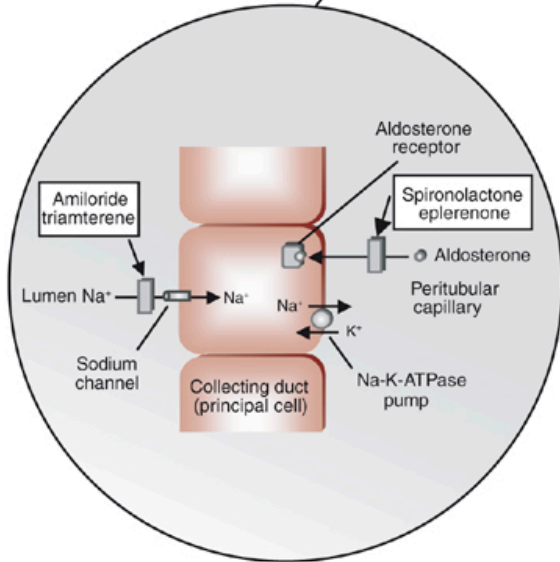
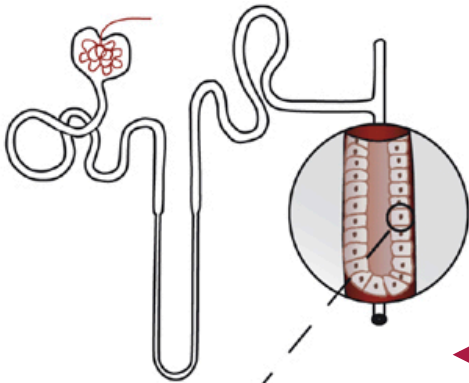
Pratica clinica: dose fissa giornaliera 0.05 - 0.2 mg



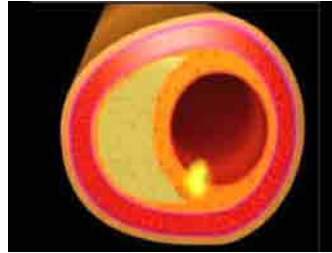
Effetti biologici dell' aldosterone



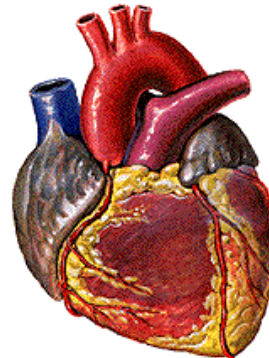
Omeostasi idro-salina



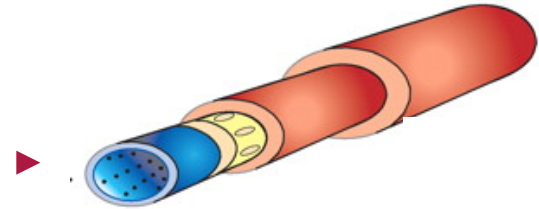
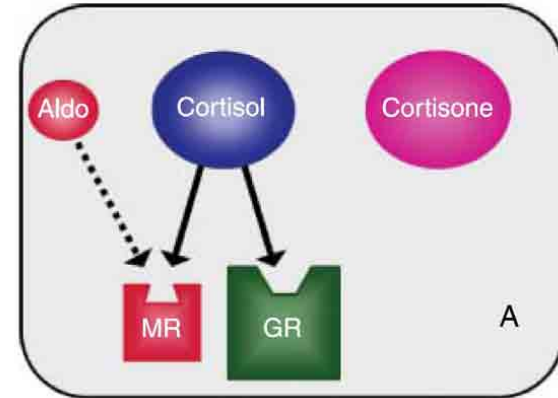
Endotelio



Aldosterone



Cuore



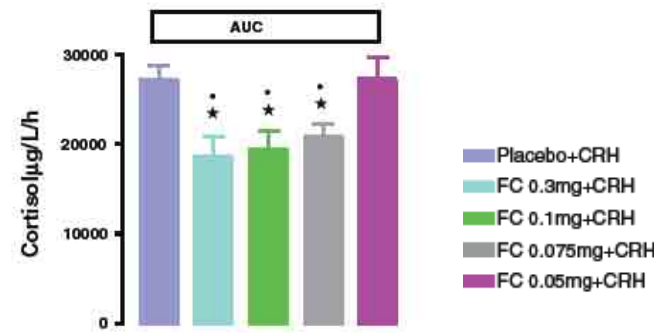
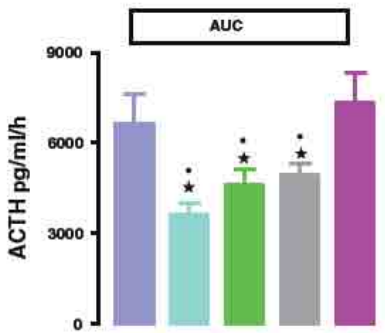
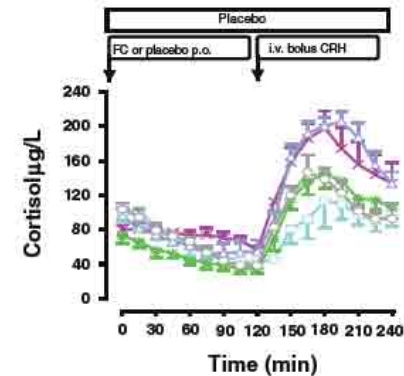
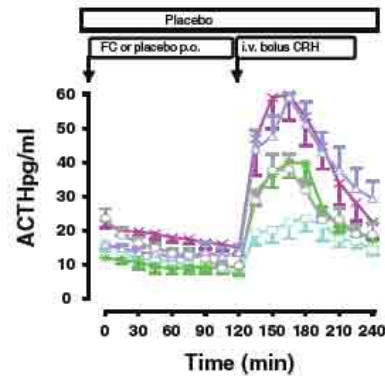
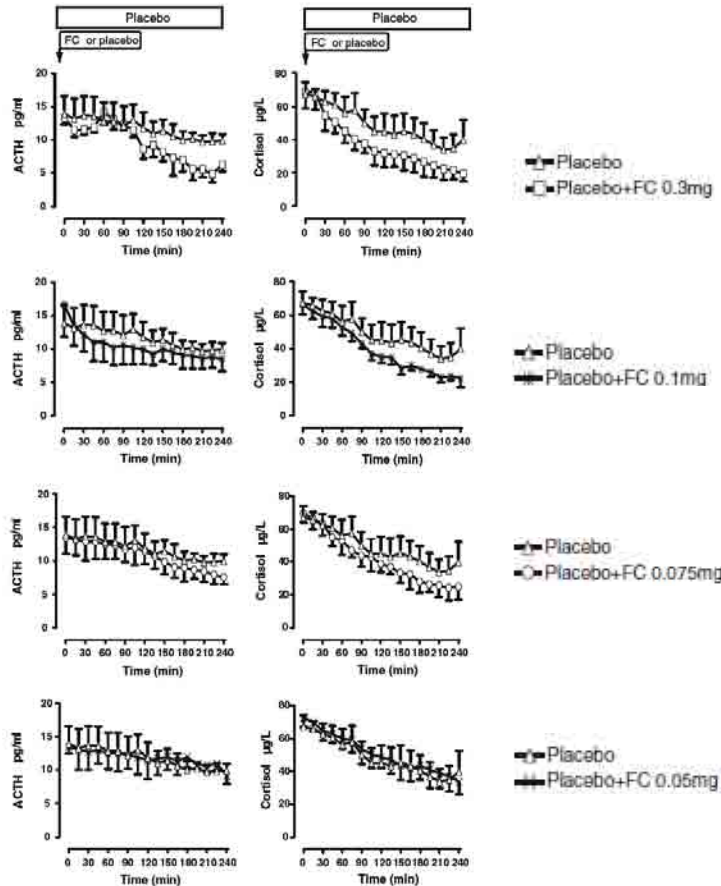
Arterie

The acute effect of fludrocortisone on basal and hCRH-stimulated hypothalamic–pituitary–adrenal (HPA) axis in humans

Ioannis Karamouzis · Rita Berardelli · Elisa Marinazzo · Valentina D'Angelo · Domenico Zinnà · Marco Alessandro Minetto · Clizia Zichi · Beatrice Fussotto · Roberta Giordano · Ezio Ghigo · Emanuela Arvat

Pituitary

DOI 10.1007/s11102-012-0435-3



◆ Placebo+CRH
 ◆ FC 0.3mg+CRH
 ◆ FC 0.1mg+CRH
 ○ FC 0.075mg+CRH
 ◆ FC 0.05mg+CRH



Monitoraggio della terapia MC



Valutazioni ematochimiche

1. Na, K
2. PRA

Valutazione clinica

1. Ricerca di segni e sintomi di sotto/sovra-dosaggio



Terapia sostitutiva DHEA



Roma,
9-11 novembre 2012

Opzioni terapeutiche

1. DHEA

Tipologia di trattamento

1. Dose fissa

Pratica clinica: terapia opzionale 25 - 50 mg



Terapia sostitutiva DHEA



Roma,
9-11 novembre 2012

Dehydroepiandrosterone replacement in women with adrenal insufficiency

Arlt W et al.

N Engl J Med 1999; 341: 1013-1020

(50 mg for 4 months)... **improves well-being and sexuality** in women with adrenal insufficiency

Improvement in mood and fatigue after dehydroepiandrosterone replacement in Addison's disease in a randomized, double blind trial

Hunt PJ et al.

J Clin Endocrinol Metab 2000; 85: 4650-4656

(DHEA 50 mg for 12 weeks)... **psychological assessment** showed significant **enhancement of self-esteem with a tendency for improved overall well-being. Mood and fatigue** also **improved** significantly, with benefit being evident in the evenings. No effects on cognitive or sexual function, body composition, lipids, or bone mineral density were observed....

Long-Term DHEA replacement in primary adrenal insufficiency: a randomized, controlled trial

Gurnell EM et al.

J Clin Endocrinol Metab 2008; 93: 400-409

(DHEA 50 mg for 12 months)... reversed ongoing loss of **bone mineral density at the femoral neck...** enhanced **total body and truncal lean mass** significantly with no change in fat mass... one **subscale of SF-36 improved significantly...** no significant benefit on fatigue or cognitive or sexual function...



Terapia sostitutiva DHEA



Roma,
9-11 novembre 2012

Improvement in mood and fatigue after DHEA replacement in Addison's disease in a randomized, double blind trial

Hunt P et al.

J Clin Endocrinol Metab 2000; 85: 4650-4656

(DHEA 50 mg for 4 months)... **no effects on** sexual function, cognition, **body composition**.... improved well-being and mood...

DHEA substitution in female adrenal failure: no impact on endothelial function and cardiovascular parameters despite normalization of androgen status

Christiansen JJ et al.

Clin Endocrinol 2007; 66: 426-433

(DHEA 50 mg for 6 months)... **did not effect cardiovascular parameters and endothelial function**...

Effects of DHEA replacement on vascular function in primary and secondary adrenal insufficiency: a randomized crossover trial

Rice SP et al.

J Clin Endocrinol Metab 2009; 94-1966-1972

(DHEA 50 mg or placebo for 12 weeks)... does **not significantly affect** measures of **arterial stiffness or endothelial function** in patients with adrenal insufficiency...

Conclusioni (1)

La terapia sostitutiva GC attualmente disponibile presenta numerosi limiti:

- ✓ **Non è in grado di mimare il ritmo circadiano del cortisolo;**
- ✓ **Non riduce i livelli circolanti di ACTH;**
- ✓ **Non normalizza la QoL;**
- ✓ **Si associa ad una aumentata mortalità (soprattutto CV) e morbilità.**

Conclusioni (2)



La terapia sostitutiva con MC esercita effetti GR-mediati ?

La terapia sostitutiva con DHEA presenta alcuni effetti positivi (QoL, sessualità, well-being, osso), ma non esiste evidenza che modifichi altri parametri importanti (rischio CV) .

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... Grazie ...