Minicorso 3

Terapia sostitutiva dell'iposurrenalismo primario e secondario

Terapia sostitutiva: fra efficacia e side-effects

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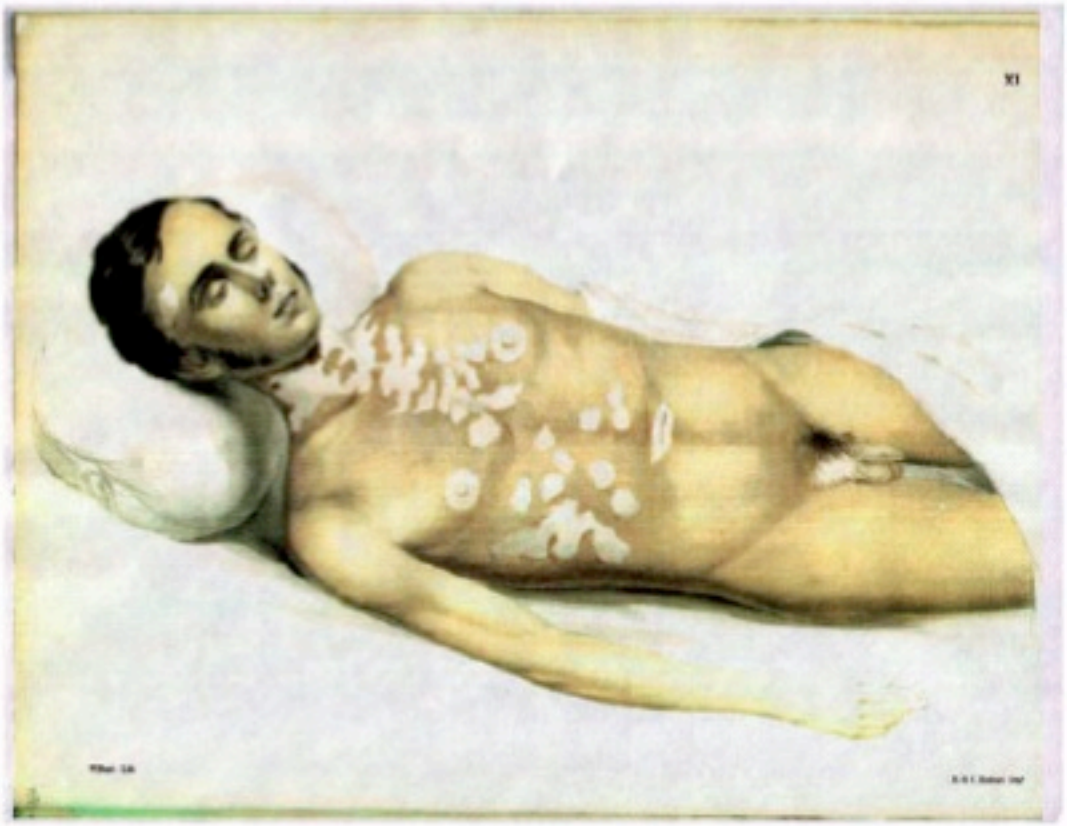
12° Congresso Nazionale AME
Associazione Medici Endocrinologi

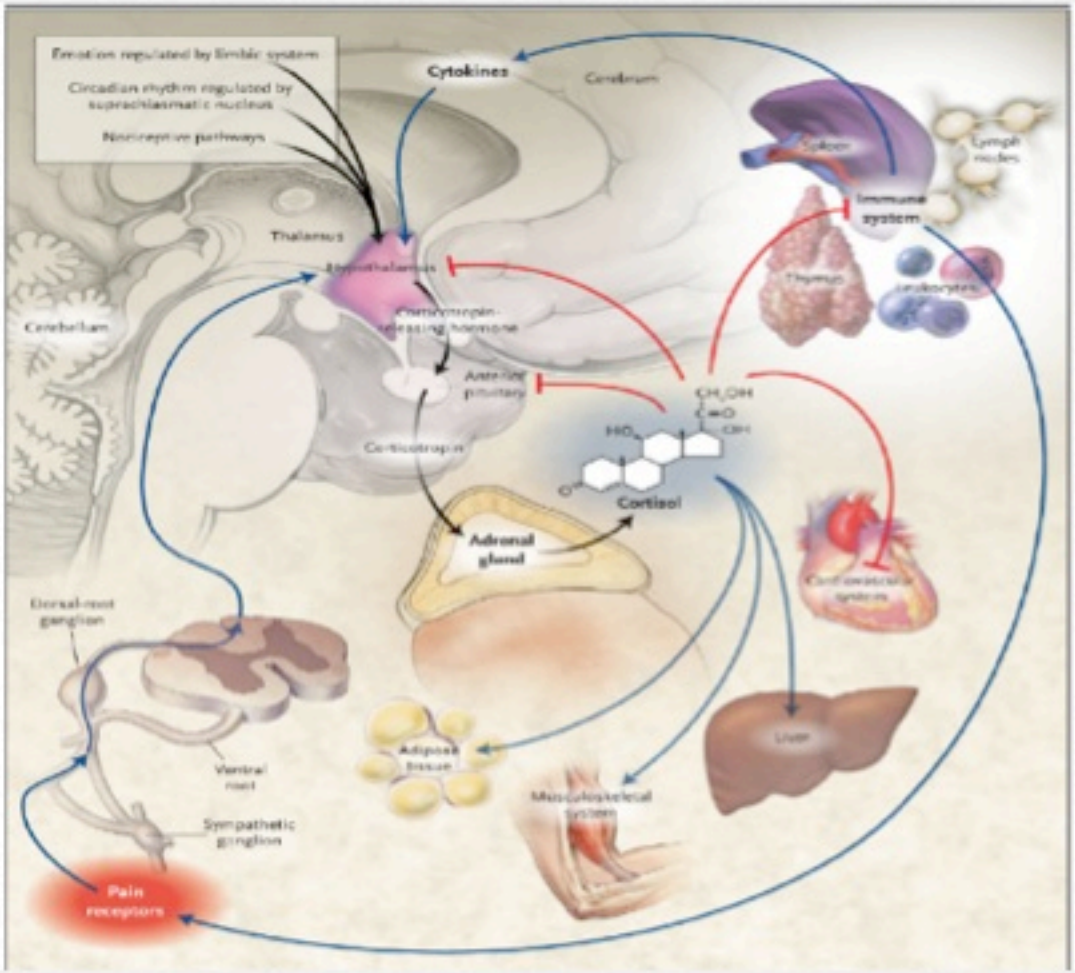
6th Joint Meeting with AACE
American Association of Clinical Endocrinologists

Bari, 7-10 novembre 2013



A drawing from Addison's original autopsy series showing pigmentation and co-existent vitiligo.

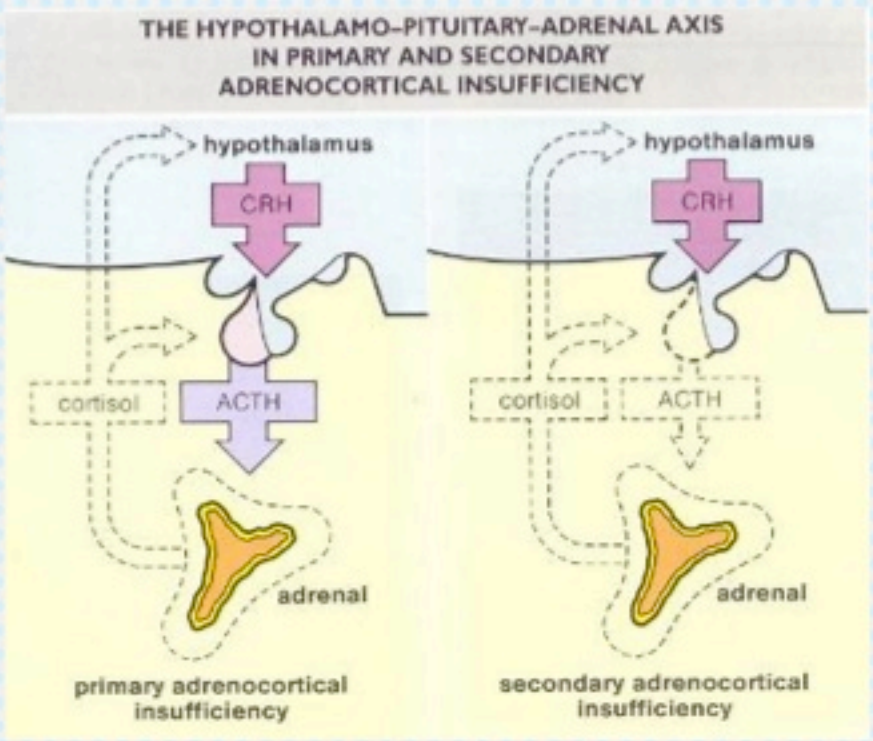
Asse HPA e ritmo circadiano

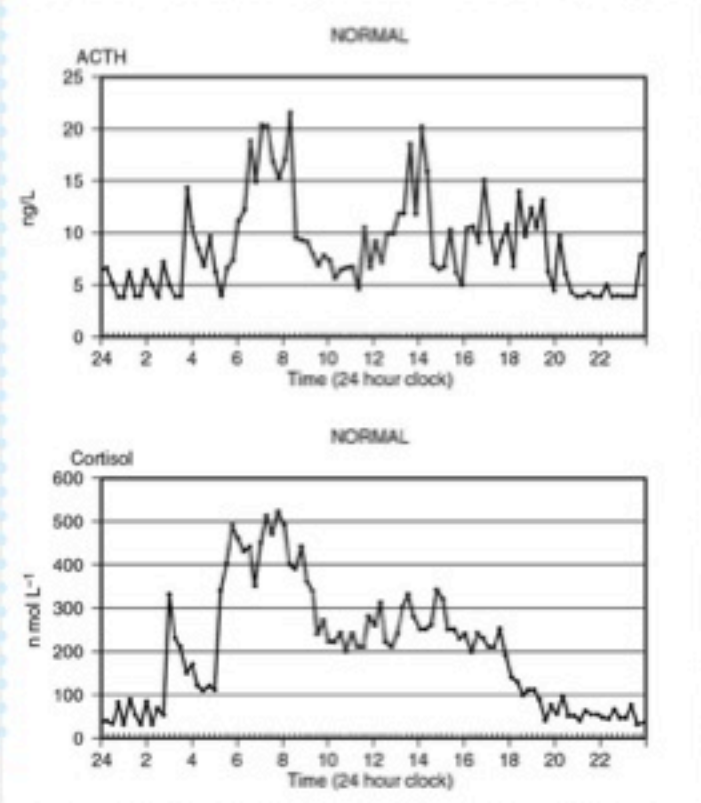


Turk Rhen, Ph.D., and John A. Cidlowski, Ph.D.

N Engl J Med 2005;353:1711-23.

Il problema della terapia





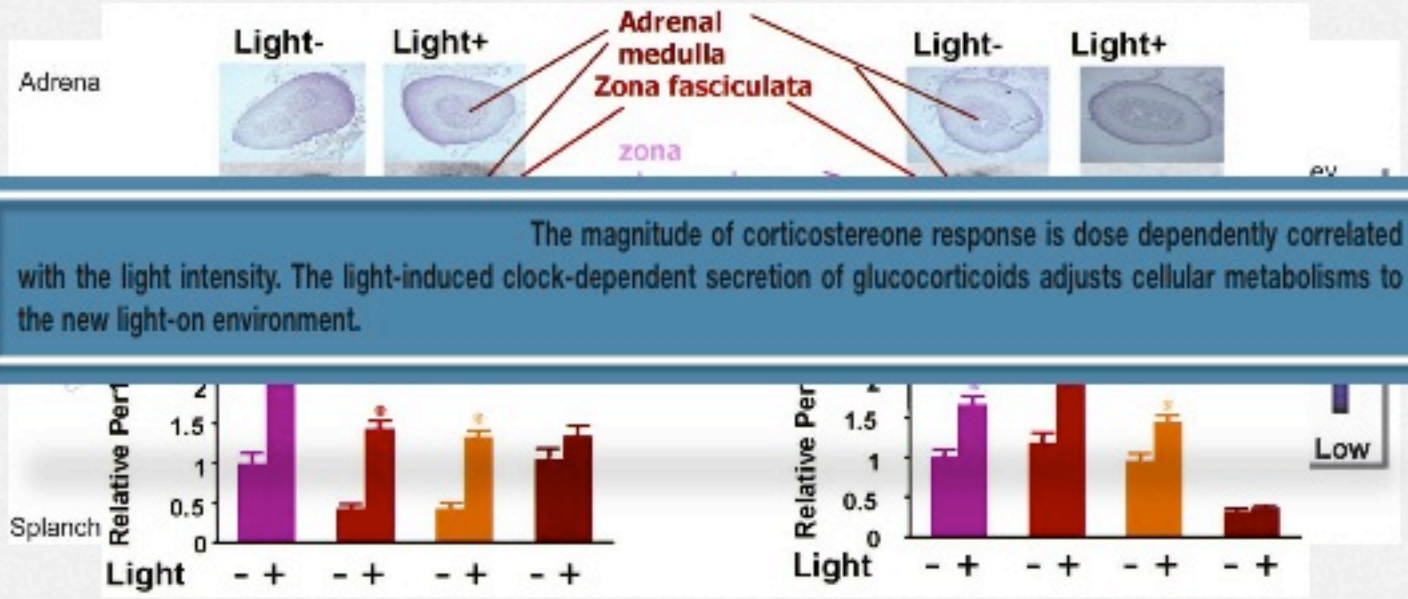
5.7-10 mg/m^2 production rate

15–25 mg idrocortisone = 25–37.5 mg cortone acetato

Light activates the adrenal gland: Timing of gene expression and glucocorticoid release

Atsushi Ishida,[1,5] Tatsushi Mutoh,[1,5] Tomoko Ueyama,[1] Hideki Bando,[1,2] Satoru Masubuchi,[1] Daiichiro Nakahara,[3] Gozoh Tsujimoto,[4] and Hitoshi Okamura[1,*]

CELL METABOLISM : NOVEMBER 2005 · VOL. 2

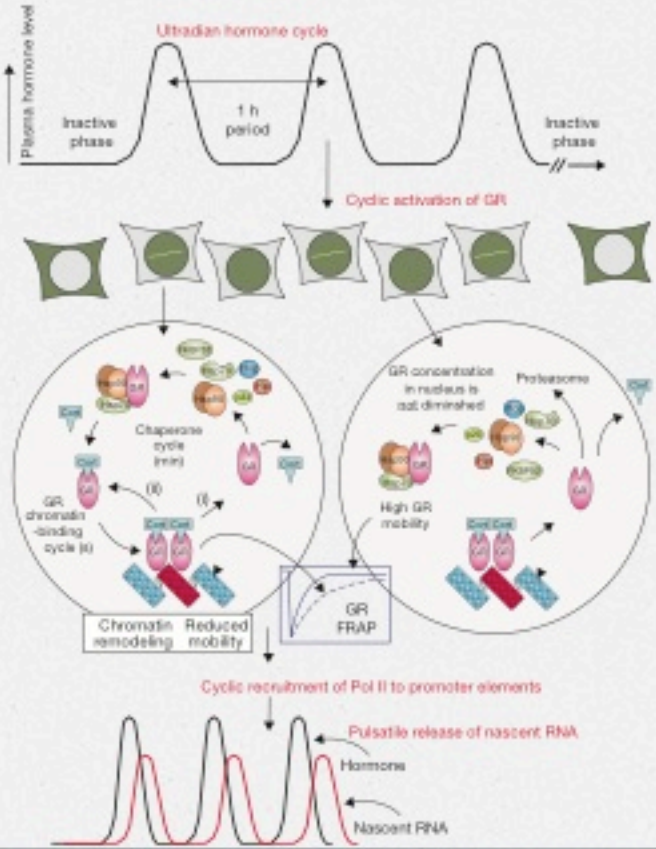


The magnitude of corticostereone response is dose dependently correlated with the light intensity. The light-induced clock-dependent secretion of glucocorticoids adjusts cellular metabolisms to the new light-on environment.

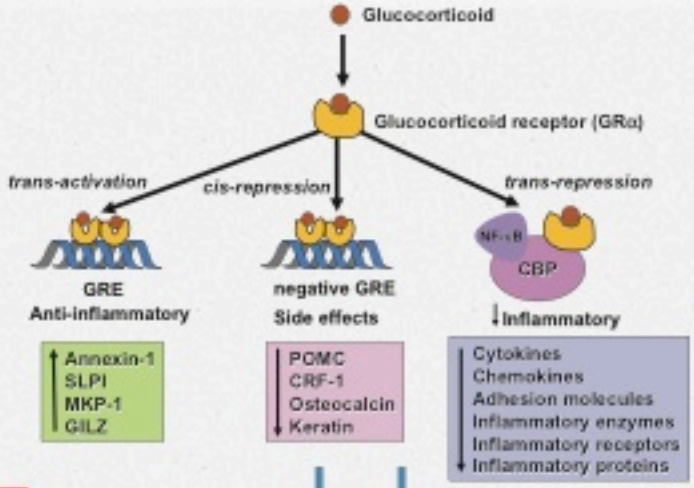
nature
cell biology

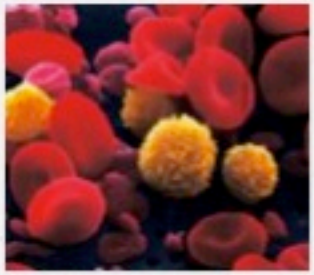
Ultradian hormone stimulation induces glucocorticoid receptor-mediated pulses of gene transcription

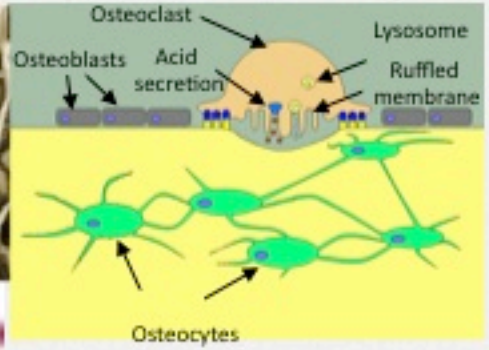
Diana A. Stavreva[1], Malgorzata Wiench[1], Sam John[1], Becky L. Conway-Campbell[2], Mervyn A. McKenna[2], John R. Pooley[2], Thomas A. Johnson[1], Ty C. Voss[1], Stafford L. Lightman[2] and Gordon L. Hager[1,3]



modificato da
Peter J Barnes
British Journal of
Pharmacology 1476-5381.2010.







Comorbidità

Comorbidità

- Addison non autoimmune
- Addison autoimmune isolato

- Sindromi polighiandolari autoimmuni

  - ✓ Ipotiroidismo
  - ✓ Insufficienza ovarica
  - ✓ Diabete mellito tipo 1
  - ✓ Ipoparatiroidismo
  - ✓ Anemia perniciosa
  - ✓ et al…….

Endocr (2010) 38:113–117
DOI 10.1007/s12020-010-9359-8

ORIGINAL ARTICLE

Co-morbidities, management and clinical outcome of auto-immune Addison's disease

Lalantha Leelarathna · Louise Breen · James K. Powrie · Stephen M. Thomas · Rustom Guzder · Barbara McGowan · Paul V. Carroll

Our data shows a high prevalence of both auto-immune and non-autoimmune co-morbidities in patients with AAD. In addition to common auto-immune diseases, patients should be screened for other cardiovascular risk factors. Further studies are needed to assess the cause of the observed increased prevalence of reduced BMD at the lumbar spine. There is a need for internationally agreed long-term management guidelines.

Problematiche della malattia isolata e delle comorbidità associate

- Addison = malattia con side-effects
- Addison + endocrinopatie = side-effects Addison + side-effects altre endocrinopatie
- Terapia Addison: scelta degli steroidi, modalità di somministrazione
- Terapia Addison + terapia endocrinopatie associate
- La terapia induce side-effects ?
  - ✓ dosaggio?
  - ✓ condizioni associate alla malattia?
  - ✓ necessità di terapie associate alla terapia sostitutiva?

malattia

terapia

Pablo Picasso

COLLECTION OF EUROPEAN MASTERS

La terapia

Farmaci glucocorticoidi disponibili

- Glucocorticoidi *short-acting*

- Glucocorticoidi *long-acting*

Farmaci mineralcorticoidi e androgeni disponibili

0.05 – 0.20 mg/die

12.5 – 50 mg/die

SPECIAL FEATURE

Approach to the Patient

The Approach to the Adult with Newly Diagnosed Adrenal Insufficiency

Wiebke Arlt JCEM'09

Clinical Endocrinology (2012) 76, 21–25 doi: 10.1111/j.1365-2265.2011.04103.x

CLINICAL QUESTION

What is the best long-term management strategy for patients with primary adrenal insufficiency?

Marcus Quinkler* and Stefanie Hahnert

Endocrine (2013) 43:514–528
DOI 10.1007/s12020-012-9835-4

REVIEW

Therapy of adrenal insufficiency: an update

Alberto Falorni · Viviana Minarelli · Silvia Morelli

Editorial

Expert Opinion

Replacement therapy in Addison's disease

Kristian Løvås† & Eystein S Husebye

Current recommended daily starting dose for hydrocortisone and cortisone acetate are 20 and 25 mg, respectively, divided into two or preferably three doses. The mineralocorticoid depletion should be treated with fludrocortisone 0.05 – 0.2 mg/day. Replacement of dehydroepiandrosterone 20 – 50 mg has been advocated in adrenal failure, but the evidence for benefit is weak.

Requisiti e problematiche per l'ottimizzazione della terapia

- ✓ Mantenimento ritmo circadiano endogeno del cortisolo
- ✓ Minima variabilità interindividuale per prevedere la dose corretta
- ✓ Facile titolazione del dosaggio
- ✓ Monitoraggio terapia: marcatore biologico azione glucocorticoidi *in vivo* (percezione dello stato di benessere individuale ?, ACTH ?, CLU ?, cortisolo sierico ?, cortisolo salivare ?)
- ✓ Rischio minimo di overtreatment
- ✓ Consensus trattamento

Schemi terapeutici

- Dose unica giornaliera
- Dose doppia giornaliera
- Dose tripla giornaliera
- Dose relativa al peso o alla superficie corporea

European Journal of Endocrinology (2009) **160** 719–729 ISSN 0804-4643

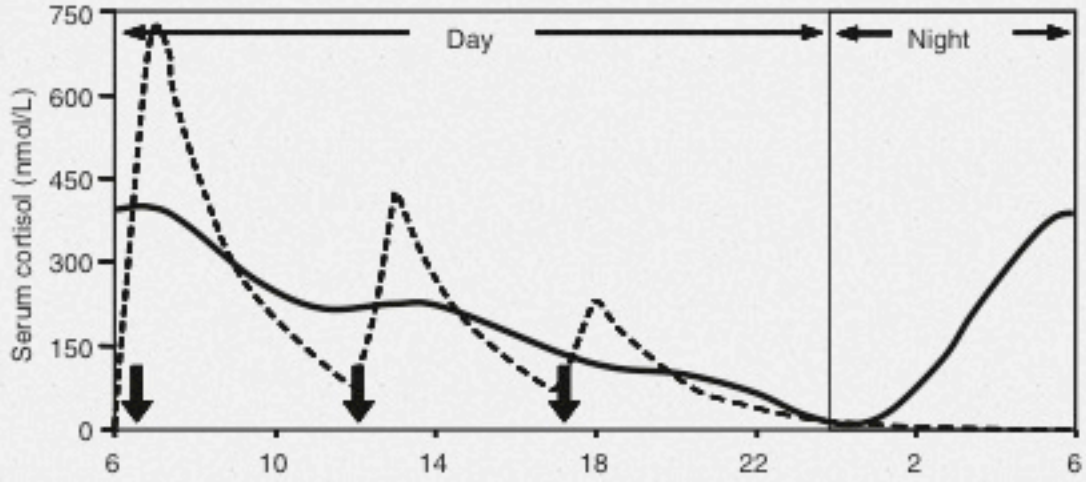
REVIEW

Inadequacies of glucocorticoid replacement and improvements by physiological circadian therapy

Miguel Debono, Richard J Ross and John Newell-Price

Patients with adrenal insufficiency need lifelong glucocorticoid replacement, but many suffer from poor quality of life, and overall there is increased mortality. Moreover, it appears that use of glucocorticoids at the higher end of the replacement dose range is associated with increased risk for cardiovascular and metabolic bone disease. These data highlight some of the inadequacies of current regimes.

La terapia nella pratica



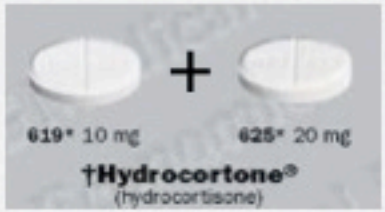
Carenza di studi che suggeriscano
l'appropriatezza di uno schema terapeutico

Effetti a lungo termine della terapia: ipotesi discordanti

I. No effetti negativi per la natura sostitutiva della terapia

II. Effetti avversi dei glucocorticoidi

Problematiche della terapia



OVER-REPLACEMENT

- IGT
- adiposità centrale
- osteoporosi
- infezioni ricorrenti
- insonnia

UNDER-REPLACEMENT

- nausea
- disappetenza
- sonnolenza
- pigmentazione
- perdita di peso
- alterazione dello stato di benessere

Effetti a lungo termine della terapia

- Aumento della mortalità
- Rischio cardiovascolare
- Alterazione metabolismo osseo

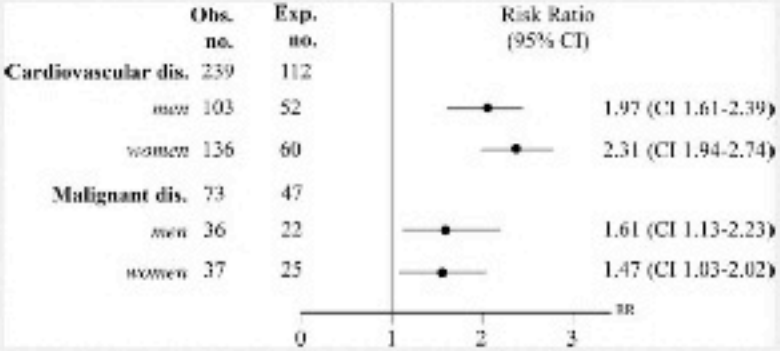
Aumento mortalità

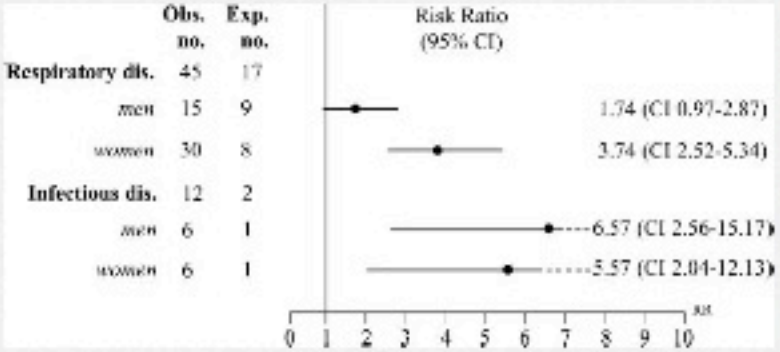
0021-972X/06/$15.00/0
Printed in U.S.A.

The Journal of Clinical Endocrinology & Metabolism 91(12):4849–4853
Copyright © 2006 by The Endocrine Society
doi: 10.1210/jc.2006-0076

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

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





Interpretation: Compared with the background population, we observed that the risk ratio for death was more than 2-fold higher in patients with Addison's disease. Cardiovascular, malignant, and infectious diseases were responsible for the higher mortality rate. (***J Clin Endocrinol Metab*** **91: 4849–4853, 2006)**

European Journal of Endocrinology (2009) **160** 233–237 ISSN 0804-4643

CLINICAL STUDY

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

Martina M Erichsen[1], Kristian Løvås[1,2], Kristian J Fougner[3], Johan Svartberg[4,5], Erik R Hauge[6], Jens Bollerslev[7,8], Jens P Berg[8,9,10], Bjarne Mella[11] and Eystein S Husebye[1,2]

Attualmente non dati a favore di un aumento della mortalità nel paziente con insufficienza corticosurrenalica sottoposto a terapia sostitutiva

Conclusion: Addison's disease is still a potentially lethal condition, with excess mortality in acute adrenal failure, infection, and sudden death in patients diagnosed at young age. Otherwise, the prognosis is excellent for patients with Addison's disease.

❑ Rischio cardiovascolare

0021-972X/97/8202-0010
Journal of Clinical Endocrinology and Metabolism
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Vol. 82, No. 8
Printed in U.S.A.

Fasting and Postprandial Lipid Abnormalities in Hypopituitary Women Receiving Conventional Replacement Therapy*

KAMAL A. S. AL-SHOUMER, KATHARINE H. COX, CAROL L. HUGHES, WILLIAM RICHMOND, AND DESMOND G. JOHNSTON

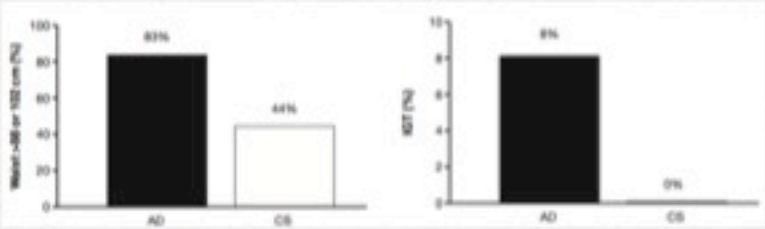
	Patients	Controls	*P* value
Triglycerides (mmol/L)			
Apolipoprotein A1 (mg/dL)[b]			
All	154 ± 14	152 ± 9	NS
Males	129 ± 14	150 ± 15	NS
Females	179 ± 19	154 ± 13	NS
Apolipoprotein B (mg/dL)[b]			
All	132 ± 6	114 ± 8	0.042
Males	129 ± 6	119 ± 13	NS
Females	135 ± 10	111 ± 9	0.048
Lipoprotein(a) (mg/dL)[c]			
All	9 (2–111)	17 (2–96)	NS
Males	28 (3–111)	29 (2–91)	NS
Females	9 (2–33)	12 (2–96)	NS

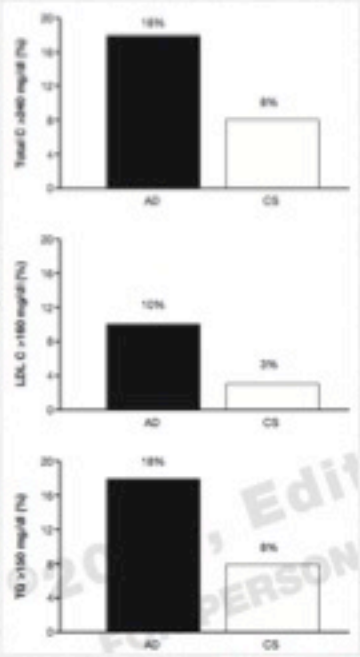
We conclude that hypopituitarism with conventional replacement therapy is associated with unfavorable fasting and postprandial lipid and lipoprotein concentrations, particularly in women. The changes may contribute to the observed increased vascular morbidity and mortality. (*J Clin Endocrinol Metab* **82:** 2653–2659, 1997)

J. Endocrinol. Invest. 32: 917-923, 2009
DOI: 10.3275/6437

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

R. Giordano[1], S. Marzotti[2], M. Balbo[3], S. Romagnoli[2], E. Marinazzo[3], R. Berardelli[3], G. Migliaretti[4], A. Benso[3], A. Falorni[2], E. Ghigo[3], and E. Arvat[3]





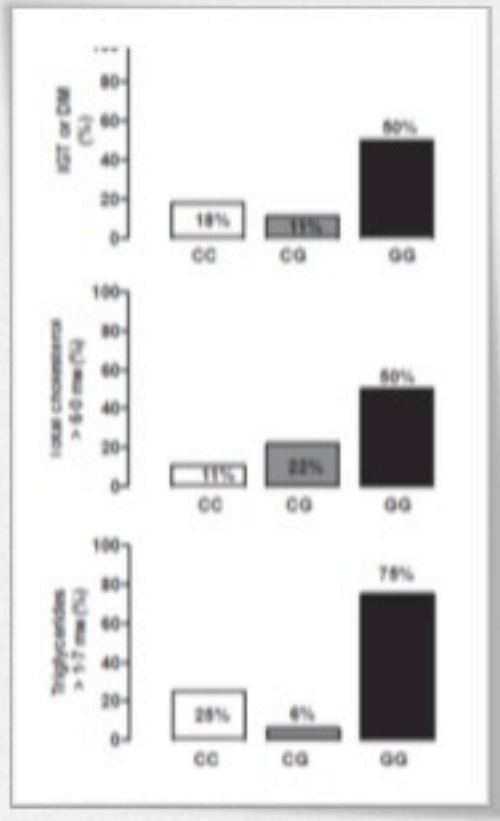
Our study shows a higher prevalence of central adiposity, impaired glucose tolerance and dyslipidemia in AD patients.

Clinical Endocrinology (2012) 77, 863–870

ORIGINAL ARTICLE

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‡



European Journal of Endocrinology (2013) **168** 403–412 ISSN 0804-4643

CLINICAL STUDY

Investigation of glucocorticoid receptor polymorphisms in relation to metabolic parameters in Addison's disease

I L Ross, N S Levitt, L Van der Merwe[1], D A Schatz[2], G Johannsson[3], C Dandara[4], T S Pillay[5] and D J Blom[6]

La terapia convenzionale glucocorticoide è gravata da una alterazione del metabolismo glicidico e lipidico che peggiora con la presenza di polimorfismi predisponenti

Questi aspetti potrebbero contribuire all'aumento di mortalità osservata in alcuni studi

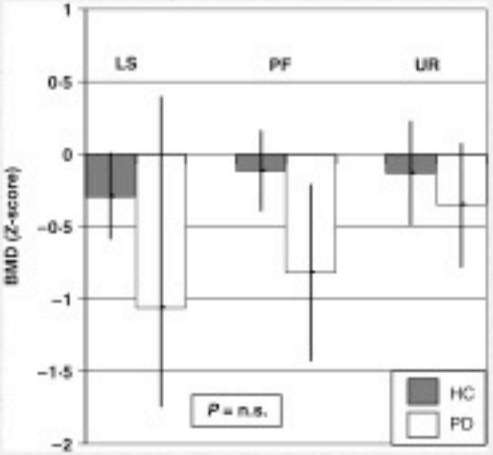
Controls	0 (0)	5 (1.00)
Patients	2 (0.12)	15 (0.88)
Hydrocortisone (mg), median (IQR)		
Patients	30.0 (25.0–30.0)	20.0 (20.0–30.0)

❑ Alterazioni del metabolismo osseo

Clinical Endocrinology (2003) **58**, 617–620

Long-term follow-up of bone mineral density in Addison's disease

Esteban Jódar*, María Pilar Ruiz Valdepeñas*, Guillermo Martínez*, Antonino Jara† and Federico Hawkins*



CONCLUSIONS Patients on long-term therapy do not show accelerated bone loss at the lumbar spine. Nevertheless, a considerable proportion of patients, mainly those treated with prednisone, showed densitometric osteoporosis.

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

TABLE 1. Clinical data and BMD of patients with PAI

PAI	Women total	Premenopausal women	Postmenopausal women	Men
Reported fractures after age of 30 yr	13/40 (32.5%)	0/1 (0%)	13/39 (33.3%)	2/19 (11.8%)
Reported spontaneous spine fractures	4/58 (6.9%)	0/18 (0%)	4/40 (10%)	1/28 (3.6%)
Smoking	4/58 (6.9%)	4/18 (22.2%)	0/40 (0%)[a]	4/28 (14.3%)

Conclusions: Adult PAI and CAH patients on low glucocorticoid doses showed normal BMD within the normal reference range. The use of longer acting prednisolone resulted in significantly lower BMD in PAI. In addition, DHEA treatment may have a beneficial effect on bone in Addison's women. (*J Clin Endocrinol Metab* 97: 85–92, 2012)

European Journal of Endocrinology (2009) **160** 993–1002 ISSN 0804-4643

CLINICAL STUDY

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

Kristian Løvås[1,2], Clara G Gjesdal[3,4], Monika Christensen[5], Anette B Wolff[1,6], Bjørg Almås[5], Johan Svartberg[7,8], Kristian J Fougner[9,10], Unni Syversen[9,10], Jens Bollerslev[11,12], Jan A Falch[11,13], Penelope J Hunt[14], V Krishna K Chatterjee[15] and Eystein S Husebye[1,2]

The common rs1045642 polymorphism in the efflux transporter *P*-glycoprotein is associated with BMD in patients with Addison's disease, and might be important for susceptibility to glucocorticoid induced osteoporosis. Glucocorticoid pharmacogenomics is likely to explain some of the variation in the effects of glucocorticoids on bone, and genotyping of the *ABCB1*, *FKBP5*, *HSD11B1* and *GR* genes might become part of future pharmacogenomic individual tailoring of both replacement and pharmacological therapy with glucocorticoids.

Clinical Endocrinology (2013) 78, 831–837 doi: 10.1111/cen.12096

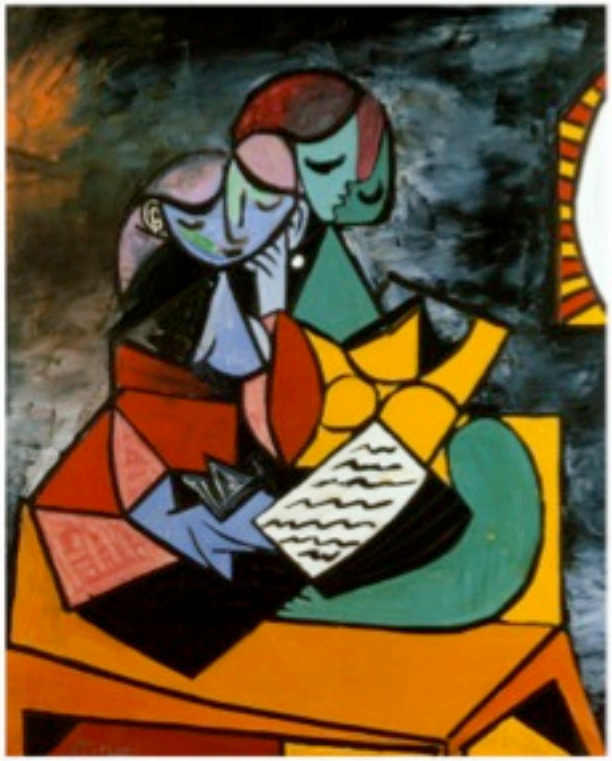
ORIGINAL ARTICLE

*Bcl*I polymorphism of the glucocorticoid receptor gene is associated with increased bone resorption in patients on glucocorticoid replacement therapy

Kathrin R. Koetz*, Elisabeth F. C. van Rossum†, Manfred Ventz*, Sven Diederich‡ and Marcus Quinkler*

La terapia con preparati short-acting a basse dosi non è associata ad osteoporosi al contrario della terapia con prednisone

Polimorfismi predisponenti ne condizionano la comparsa



Qualità della vita e
percezione dello stato di benessere

Physical Functioning

Role Physical

General Health

Vitality

Social Functioning

Role Emotional

	PF	RP	BP	GH	VT	SF	RE	MH
(a) Total								
Norm								2255)
								0·34
Patients								(n = 44)
Mean	77·6 ± 3·22	48·8 ± 6·76	72·4 ± 4·11	51·8 ± 3·86	50·2 ± 4·05	76·9 ± 4·13	65·1 ± 5·33	80·3 ± 1·82
25 percentile	65	0	51	30	25	50	33	72
Median	80	25	74	47	53	82	67	80
75 percentile	95	100	100	72	70	100	100	88
p*	0·06	0·001	0·9	0·001	0·05	0·07	0·014	

CONCLUSIONS Patients with Addison's disease under replacement therapy with cortisone acetate and fludrocortisone have reduced general health perception and vitality, and increased fatigue. .....

..... Thus, there might be potential for further refinement of replacement therapy.

0021-972X/07/$15.00/0
Printed in U.S.A.

The Journal of Clinical Endocrinology & Metabolism 92(10):3912–3922

doi: 10.1210/jc.2007-0685

Impaired Subjective Health Status in 256 Patients with Adrenal Insufficiency on Standard Therapy Based on Cross-Sectional Analysis

Stefanie Hahner, Melanie Loeffler, Martin Fassnacht, Dirk Weismann, Ann-Cathrin Koschker, Marcus Quinkler, Oliver Decker, Wiebke Arlt, and Bruno Allolio

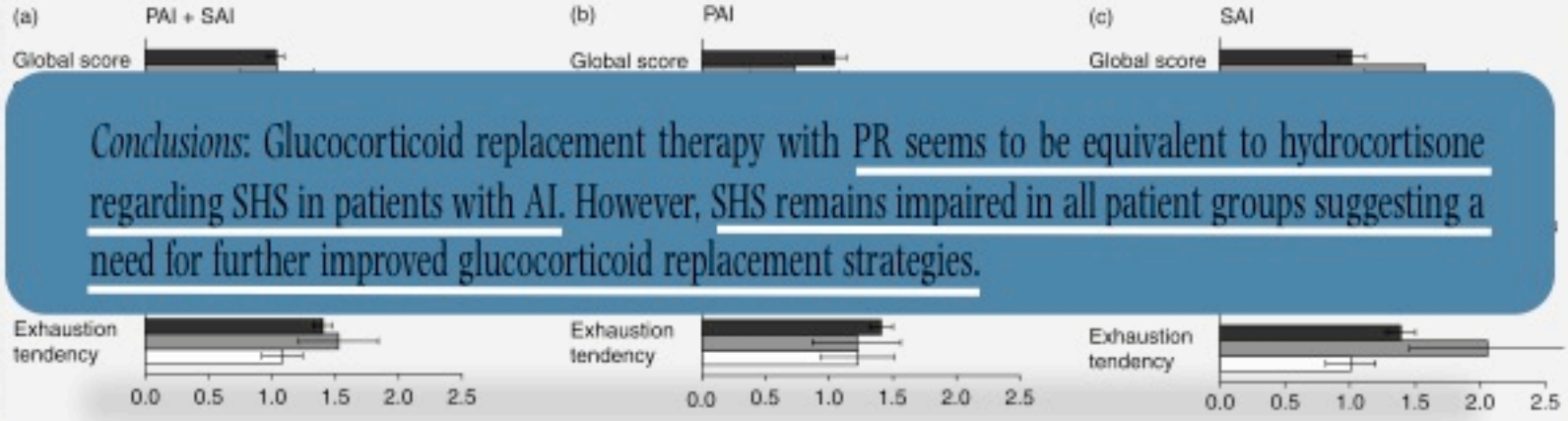
In conclusion, patients with both primary and secondary AI suffer from significantly impaired health-related subjective health status despite current standard replacement therapy, with a high percentage of patients being out of work and receiving disablement pensions. Importantly, this impairment is largely independent of concomitant endocrine and nonendocrine disease. In this cross-sectional, noninterventional study, patients receiving DHEA or GH replacement did not have improved measures of health-related subjective health status. This may indicate that current replacement regimens in AI are not suitable for reestablishing a normal health-related subjective health status in AI patients

European Journal of Endocrinology (2008) **159** 811–817 ISSN 0804-4643

CLINICAL STUDY

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

Benjamin Bleicken*, Stefanie Hahner[1,*], Melanie Loeffler[1], Manfred Ventz, Bruno Allolio[1] and Marcus Quinkler



Conclusions: Glucocorticoid replacement therapy with PR seems to be equivalent to hydrocortisone regarding SHS in patients with AI. However, SHS remains impaired in all patient groups suggesting a need for further improved glucocorticoid replacement strategies.

Forss et al. BMC Endocrine Disorders 2012, 12:8
http://www.biomedcentral.com/1472-6823/12/8

BMC
Endocrine Disorders

RESEARCH ARTICLE Open Access

Current practice of glucocorticoid replacement therapy and patient-perceived health outcomes in adrenal insufficiency - a worldwide patient survey

M Forss[1*], G Batcheller[1], S Skrtic[2] and G Johannsson[3]

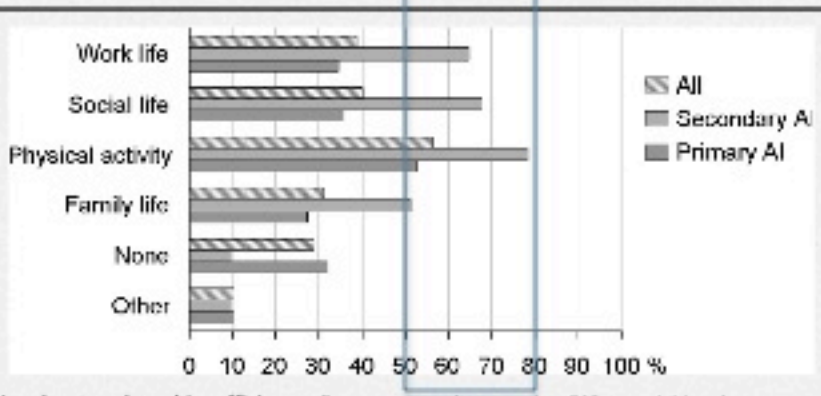


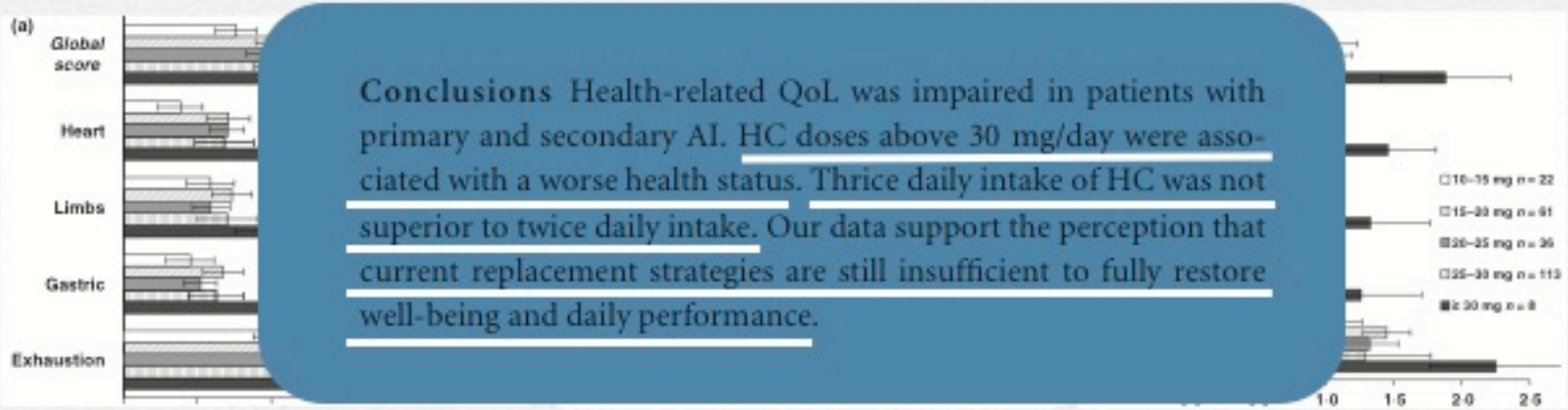
Figure 1 Change in activities due to adrenal insufficiency. Responses to the question "What activities do you need to alter due to your adrenal insufficiency"? in an international patient survey. A total of 1001 subjects responded to this question.

Clinical Endocrinology (2010) 72, 297–304 doi: 10.1111/j.1365-2265.2009.03596.x

ORIGINAL ARTICLE

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

Benjamin Bleicken*,**, Stefanie Hahnert,**, Melanie Loefflert, Manfred Ventz*, Oliver Deckert, Bruno Allolio† and Marcus Quinkler*



Conclusions Health-related QoL was impaired in patients with primary and secondary AI. 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. Our data support the perception that current replacement strategies are still insufficient to fully restore well-being and daily performance.

In sintesi

- ✓ la qualità della vita risulta alterata sia nell'insufficienza surrenalica primitiva che secondaria
  (anche con la supplementazione di DHEA e GH)
- ✓ no differenze tra prednisone e idrocortisone nella qualità della vita
- ✓ peggiore qualità della vita lavorativa, sociale, e fisica nell'insufficienza secondaria
- ✓ la triplice somministrazione della terapia peggiora la qualità della vita
- ✓ necessità di un nuovo schema terapeutico

Development of a Disease-Specific Quality of Life Questionnaire in Addison's Disease

Kristian Løvås, Suzanne Curran, Marianne Øksnes, Eystein S. Husebye, Felicia A. Huppert, and V. Krishna K. Chatterjee

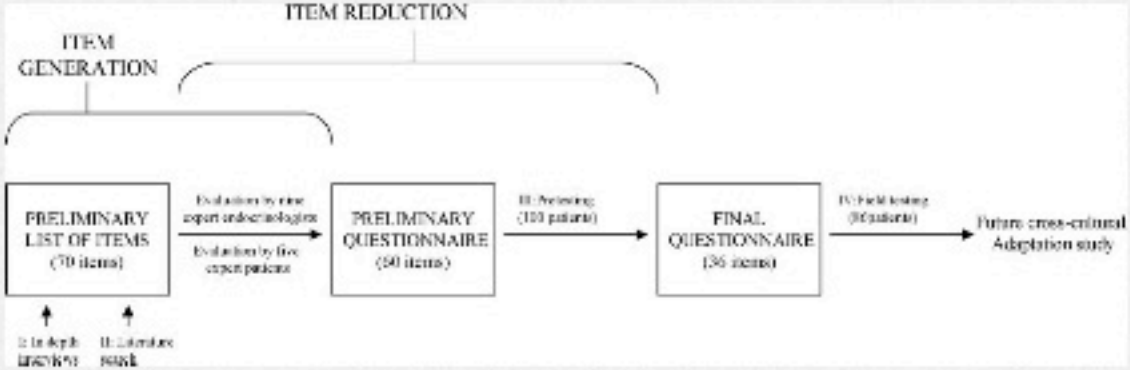


FIG. 1. Flow chart of study design.

Conclusions: We envisage AddiQoL having utility in trials of hormone replacement and management of patients with Addison's disease, analogous to similar questionnaires in GH deficiency (AGHDA) and acromegaly (AcroQoL). (***J Clin Endocrinol Metab*** **95: 545–551, 2010)**

ORIGINAL ARTICLE

Endocrine Research

Quality of Life in European Patients with Addison's Disease: Validity of the Disease-Specific Questionnaire AddiQoL

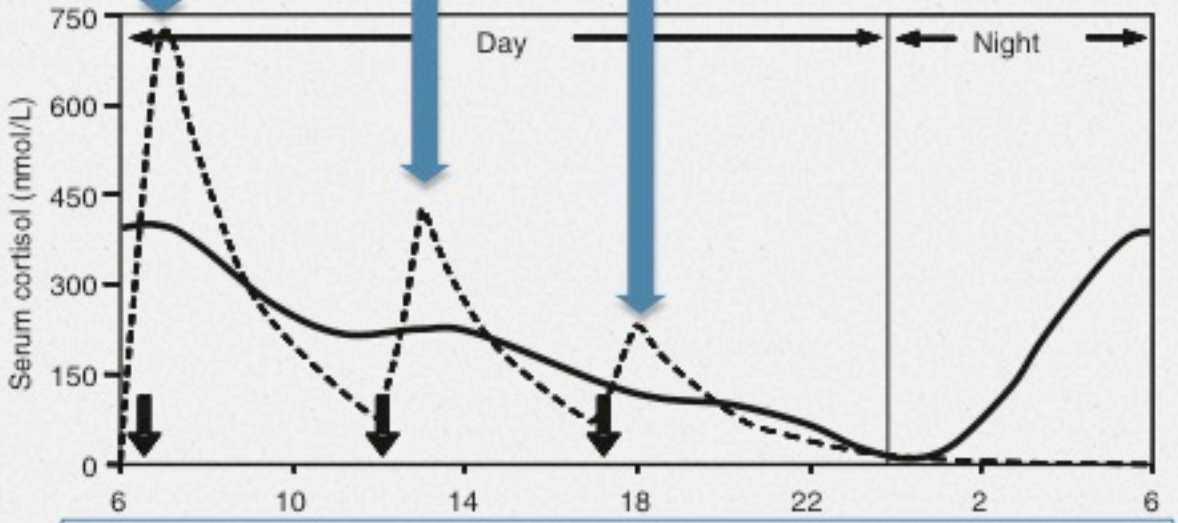
Marianne Øksnes, Sophie Bensing, Anna-Lena Hulting, Olle Kämpe, Annika Hackemann, Gesine Meyer, Klaus Badenhoop, Corrado Betterle, Anna Parolo, Roberta Giordano, Alberto Falorni, Lucyna Papierska, Wojciech Jeske, Anna A. Kasperlik-Zaluska, V. Krishna K. Chatterjee, Eystein S. Husebye, and Kristian Løvås

Conclusion: The validation process resulted in a revised 30-item AddiQoL questionnaire and an eight-item AddiQoL short version with good psychometric properties and high reliability. (***J Clin Endocrinol Metab*** **97: 568–576, 2012)**

Limiti della terapia

Profilo tipo di un pz sottoposto a terapia sostitutiva con glucocorticoidi

Picchi sovrafisiologici 90-120' dopo la terapia

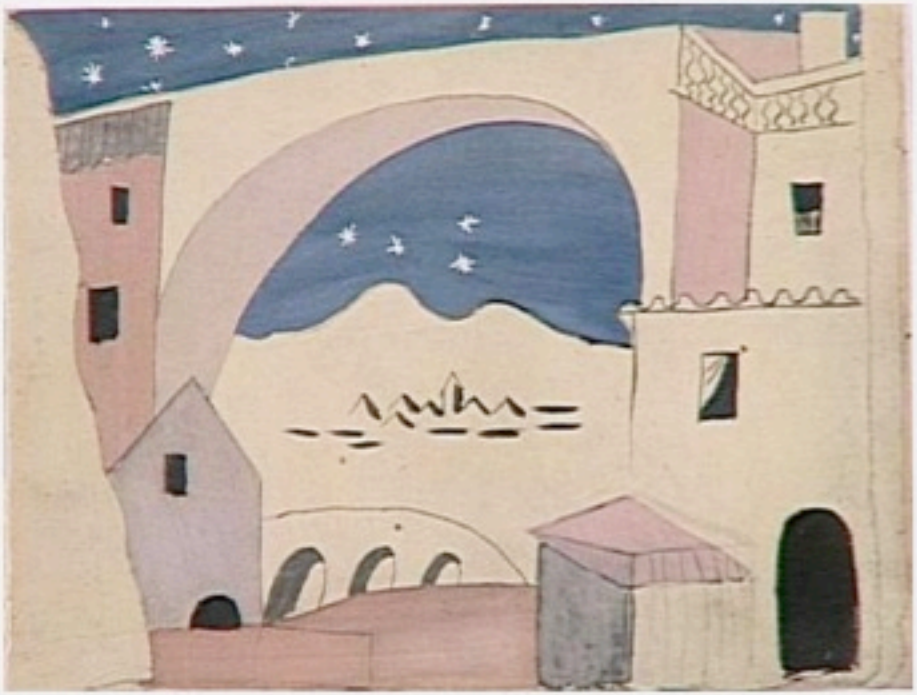


Livelli di cortisolo ridotti o indosabili prima del risveglio e delle altre somministrazioni

Criticità

- mancato rispetto del ritmo circadiano responsabile della mancata compliance del pz

- probabile sovrastima della terapia sostitutiva come causa degli effetti collaterali indotti a lungo termine



Prospettive future

Best Practice & Research Clinical Endocrinology & Metabolism 23 (2009) 221–232

Contents lists available at ScienceDirect

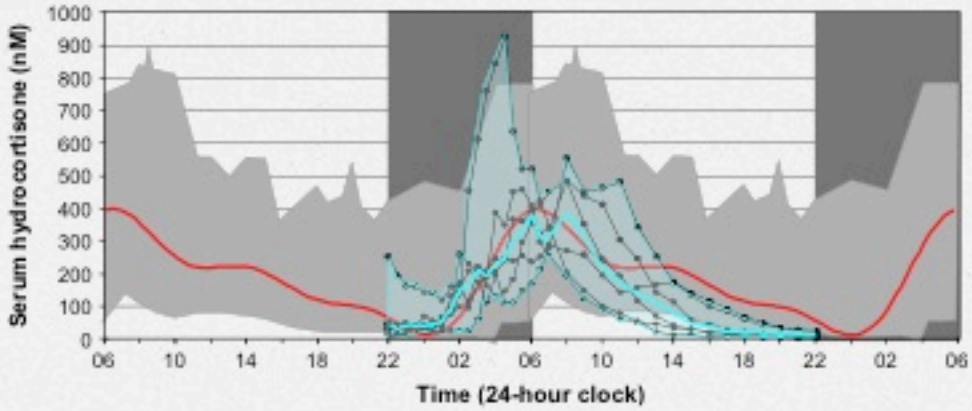
Best Practice & Research Clinical Endocrinology & Metabolism

journal homepage: www.elsevier.com/locate/beem

7

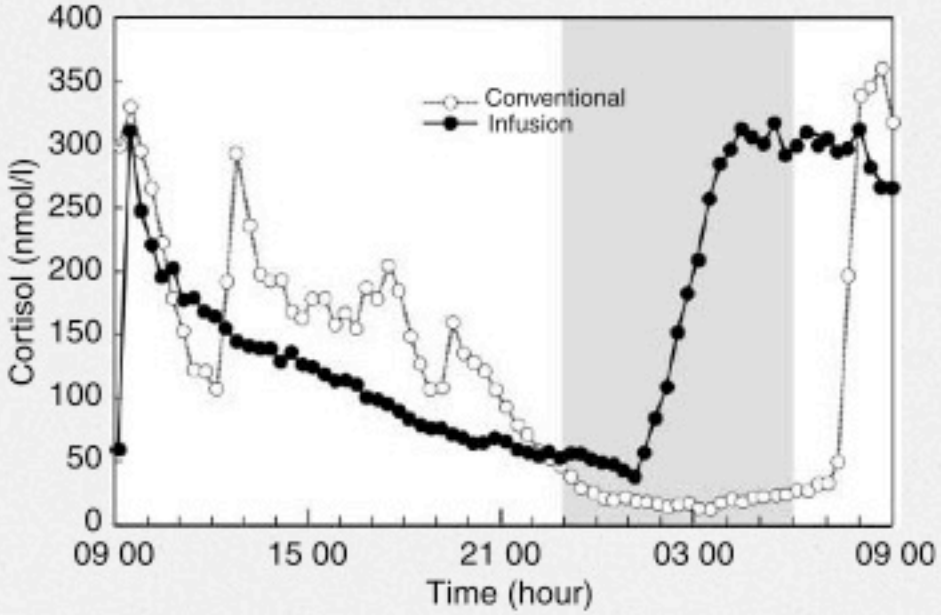
Novel strategies for hydrocortisone replacement

M. Debono, MRCP, Academic Clinical Fellow Endocrinology, J. Newell Price, MA, PhD, FRCP, Senior Lecturer in Endocrinology and Honorary Consultant Physician, Richard J. Ross, MD, FRCP, Head of Section Endocrinology and Reproduction, and Professor of Endocrinology *



Circadian hydrocortisone infusions in patients with adrenal insufficiency and congenital adrenal hyperplasia

Z Merza, A Rostami-Hodjegan, A Memmott, A Doane, V Ibbotson, J Newell-Price, GT Tucker, RJ Ross
Clin Endocrinol 65 (16) '06



European Journal of Endocrinology (2007) **157** 109–112 ISSN 0804-4643

CLINICAL STUDY

Continuous subcutaneous hydrocortisone infusion in Addison's disease

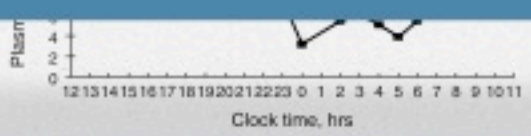
Kristian Løvås[1,2] and Eystein S Husebye[1,2]

Indicazioni:

- ✓ pz con difficile controllo malattia con terapia orale

Limiti:

- ✓ presidi sperimentali che necessitano di ulteriori validazioni

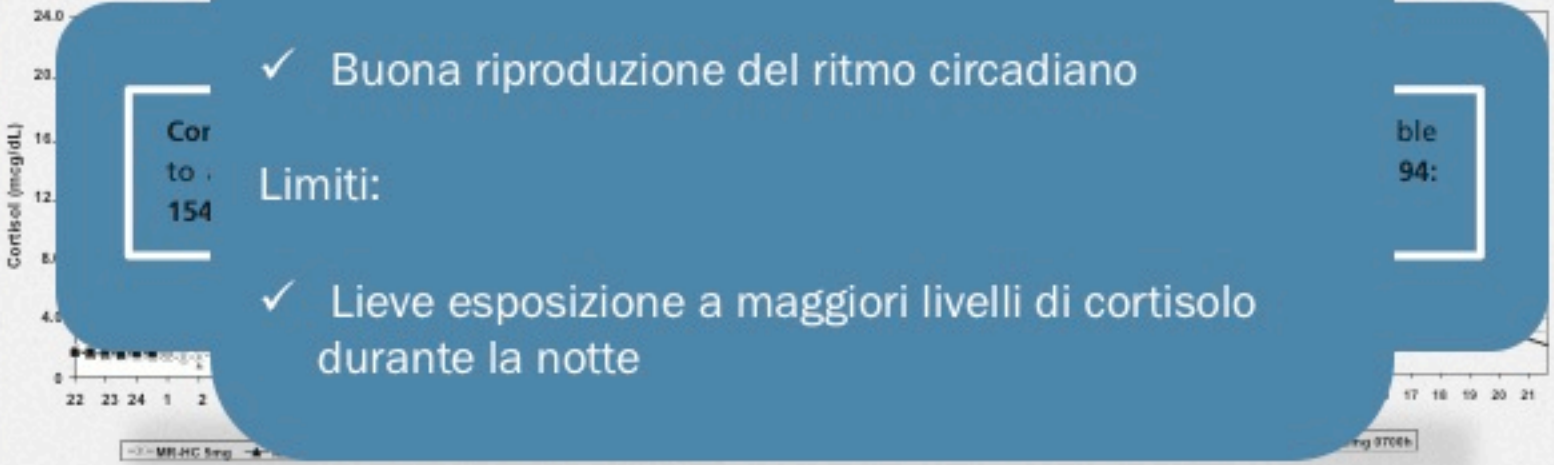


ORIGINAL ARTICLE

Endocrine Care

Modified-Release Hydrocortisone to Provide Circadian Cortisol Profiles

Miguel Debono, Cyrus Ghobadi, Amin Rostami-Hodjegan, Hiep Huatan, Michael J. Campbell,



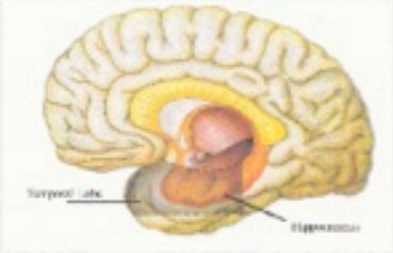
Efficacia:

- ✓ Buona riproduzione del ritmo circadiano

Limiti:

- ✓ Lieve esposizione a maggiori livelli di cortisolo durante la notte

- Disturbi del sonno



European Journal of Endocrinology (2003) **148** 449–456

CLINICAL STUDY

Sleep disturbances in patients with Addison's disease

Kristian Løvås, Eystein S Husebye, Fred Holsten[1] and Bjørn Bjorvatn[2]

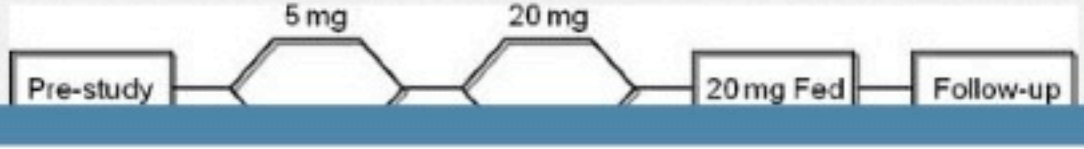
	Difficulties falling asleep	Repeated awakenings	Early morning awakenings	Tired or sleepy during daily activities
Gender				
Women ($n = 34$)	6	16	23	48
Men ($n = 26$)	23	12	17	31
P-value[1]	0.08	> 0.20	> 0.20	> 0.20
Age				
Age < 34 years ($n = 15$)	27	13	7	40
Age 35–50 years ($n = 23$)	8	9	14	35
Age > 50 years ($n = 22$)	14	18	39	47
P-value[2]	0.15	> 0.20	> 0.20	> 0.20
Disease category				
Addison's disease ($n = 26$)	12	13	17	46
APS I ($n = 7$)	29	0	29	43
APS II ($n = 27$)	11	11	22	35
P-value[3]	> 0.20	> 0.20	> 0.20	> 0.20
Dosage of cortisone acetate*				
Last dose at 1800 h or before ($n = 14$)	21	7	0	29
Last dose after 1800 h ($n = 11$)	18	30	40	50
P-value[4]	> 0.20	0.18	> 0.20	> 0.20
All ($n = 60$)	13	14	20	40

European Journal of Endocrinology (2009) **161** 119–130 ISSN 0804-4643

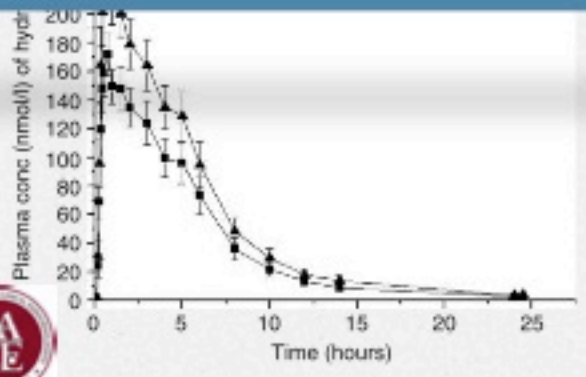
CLINICAL STUDY

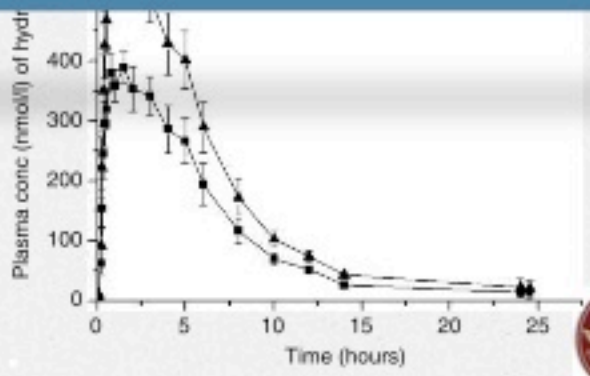
Improving glucocorticoid replacement therapy using a novel modified-release hydrocortisone tablet: a pharmacokinetic study

Gudmundur Johannsson[1], Ragnhildur Bergthorsdottir[1], Anna G Nilsson[1], Hans Lennernas[3], Thomas Hedner[2] and Stanko Skrtic[2]



Conclusion: The dual release hydrocortisone tablet with once-daily administration produced a diurnal plasma cortisol profile mimicking the physiological serum cortisol profile.



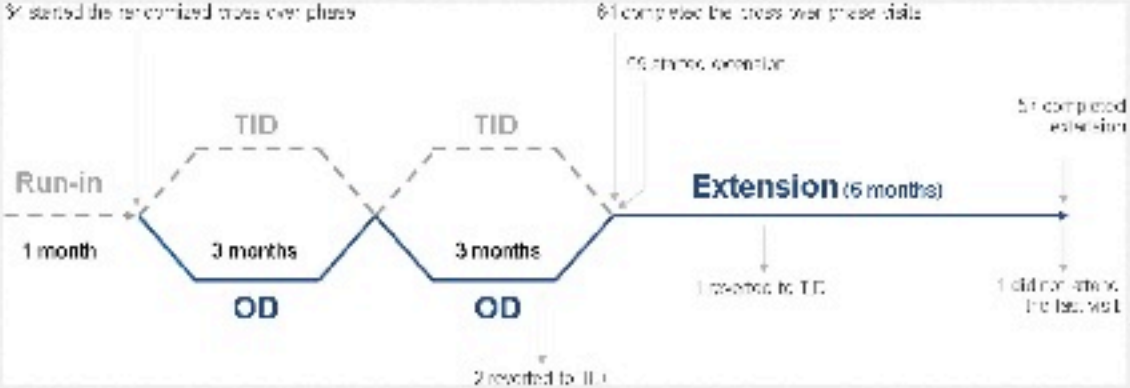


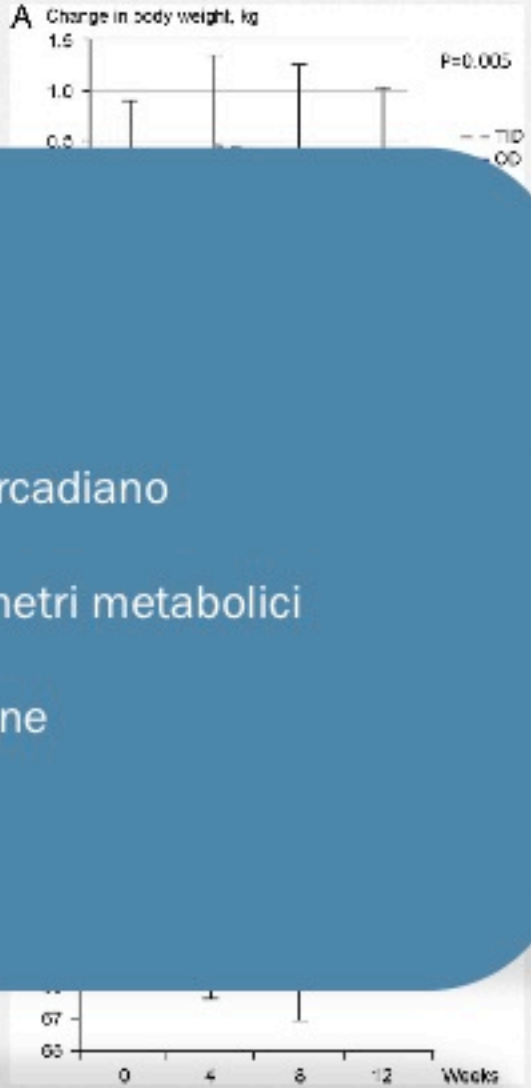
ORIGINAL ARTICLE

Endocrine Research

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





Vantaggi:

- ✓ riproduzione ritmo circadiano
- ✓ miglioramento parametri metabolici
- ✓ unica somministrazione

SPECIAL FEATURE

Approach to the Patient

The Approach to the Adult with Newly Diagnosed Adrenal Insufficiency

Wiebke Arlt JCEM'09

Riduzione della posologia nei pz ipertesi controllando i livelli elettrolitici

DOI 10.1007/s12020-012-9835-4

REVIEW

Therapy of adrenal insufficiency: an update

Alberto Falorni · Viviana Minarelli · Silvia Morelli

- **DHEA *pro***
  - ✓ miglioramento benessere fisico e psicologico (anche nei bambini)
  - ✓ miglioramento libido
  - ✓ effetto antidepressivo (neurosteroide)
  - ✓ immunomodulatore
  - ✓ miglioramento della densità minerale ossea

ORIGINAL ARTICLE

Endocrine Care

Long-
Insuff

Adrenal
rial

Eleanor M.
Eleanor M.
V. Krishna

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of DHEA treatme

Conclusion: Altho

osage adjustment, are

desirable, our res

reatment in Addison's

disease. (*J Clin En*

- **DHEA *contro***
  - ✓ acne, seborrea spesso transitorie
  - ✓ dati discordanti
  - ✓ indisponibilità di preparazioni farmaceutiche controllate

Come dobbiamo trattare i pazienti ?

Glucocorticodi replacement

- Riproduzione del ritmo circadiano del cortisolo
- Somministrazione glucocorticoidi ad azione short-acting
- Evitare over- e under-treatment
- Considerare terapia delle comorbidità
- Considerare interferenti

Mineralcorticoidi replacement

- Possibilità di riduzione della terapia nei pz ipertesi ma controllo elettrolitico costante
- Aumento della posologia nell'ultimo trimestre di gravidanza

Androgeni replacement

- Riservare terapia con DHEA a pazienti (prevalentemente donne) con riduzione della libido, cute ipoidratata e depressione