Lunedì 10 Aprile 2017

17:45-19:00

SIMPOSIO 2

L' INSUFFICIENZA SURRENALICA SECONDARIA

Moderatori: Gianluca Aimaretti, Alfredo Scillitani

LA TERAPIA CON GLUCOCORTICOIDI: FARMACI CONVENZIONALI E NUOVE PROSPETTIVE TERAPEUTICHE

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GC REPLACEMENT TREATMENT

AN "IDEAL DRUG" SHOULD:

- normalize the standardized mortality ratio
- avoid over-replacement: metabolic syndrome, cardiovascular disease, osteoporosis
- improve Quality of Life & treatment compliance
- avoid adrenal crisis
- restore and mimic the normal physiological cortisol circadian rhythm

Aulinas A. & Webb S.M. Expert Rev. Pharmacoecon. Outcomes Res. 2014

HORMONAL REPLACEMENT IN HYPOPITUITARISM IN ADULTS: AN ENDOCRINE SOCIETY CLINICAL PRACTICE GUIDELINE

GLUCOCORTICOIDS

- **HC 15–20 mg/day in single or divided doses:** patients using divided doses should take the highest dose in the morning at awakening and the second in the afternoon (two-dose regimen) or the second and third at lunch and late afternoon, respectively (three-dose regimen)

- **Longer-acting GCs only in selected cases** (non-availability, poor compliance, convenience)

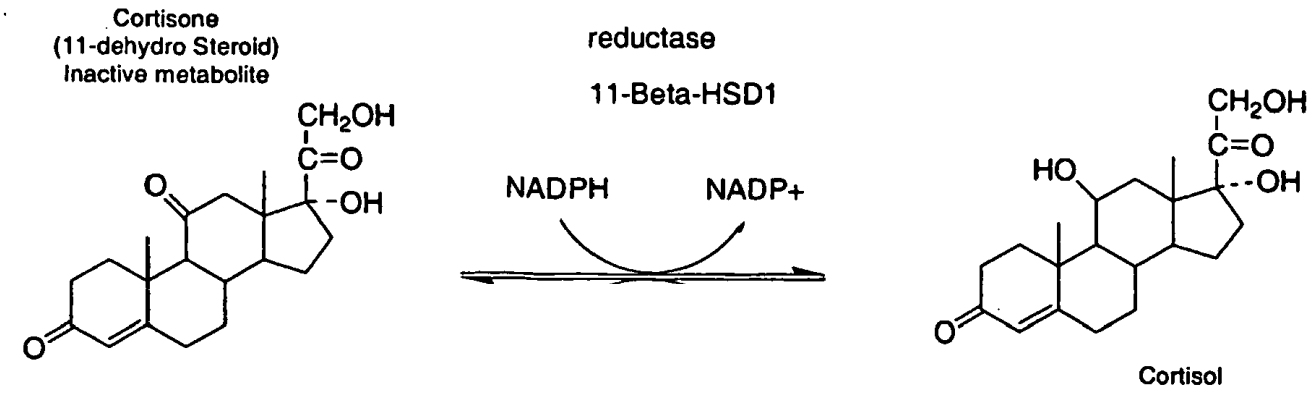
- **Clinicians should teach all AI patients regarding stress-dose and emergency GC administration: immediate parenteral injection of 50 –100 mg HC**

- **Against using fludrocortisone in patients with secondary AI**

Fleseriu et al, JCEM 2016

➢In some European countries, including Italy, HC is not easily available

➢The preferred choice is cortisone acetate (CA) at 20–25 mg total daily dose, that is a pro-drug converted in Cortisol by 11bHSD1[1]



➢Some authors oppose the use of CA, since 11bHSD1 deficiency/variable activity may result in an inactive/unpredictable replacement therapy [2,3]

➢Compared with HC, CA presents a lower cortisol peak and possible delayed cortisol clearance, which might reduce circulating cortisol fluctuations[4]

1. Oelkers Ann Endocrinol 2001; 2. Tomlison Endocr Rev 2004; 3. Nordenström JCEM 1999; 4. Nickelsen Exp Clin Endocr 1983

GC DOSES MANAGEMENT

- **Daily cortisol production in healthy individuals is about 5–10 mg/m^2 BSA corresponding to approximately 15–20 mg/day of HC**

- **No reliable marker to determine exact GC needs is available, initial dose requirements are largely estimated**

- **Further dose adjustments depend on:**

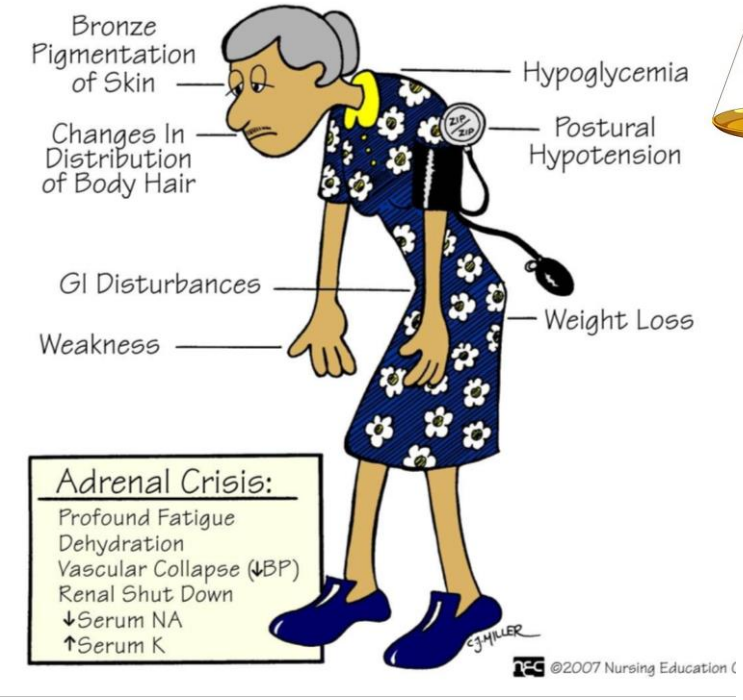
  1. **Clinical judgment**
     - **Over**-replacement: Edema, weight gain, insomnia, Cushingoid symptoms & signs (metabolic and cardiovascular diseases, osteoporosis and bone fractures)
     - **Under**-replacement: Weight loss, hypotension, fatigue, myalgia, nausea, lethargy, poor appetite
  2. **Patient preference**
  3. **Comorbidities & QoL**

- **A high proportion of patients on "conventional" corticosteroid replacement therapy for AI are over-treated or on inappropriate replacement regimens**

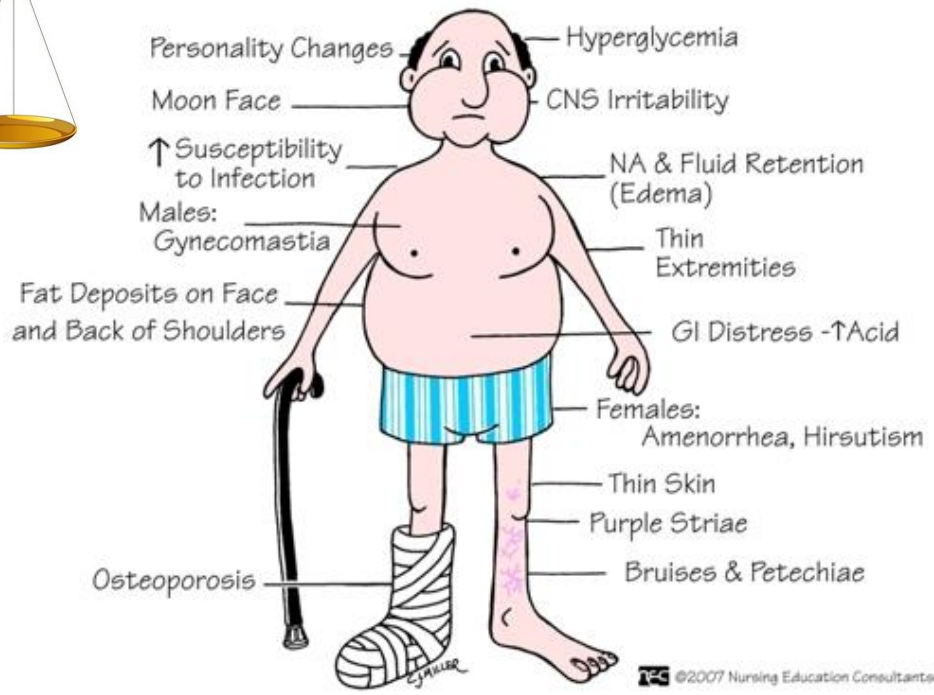
Fleseriu et al, JCEM 2016

THE CHALLENGE

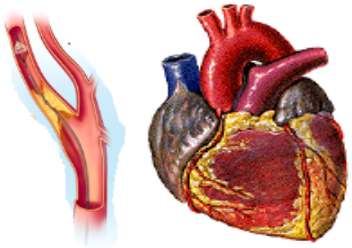
UNDER REPLACEMENT

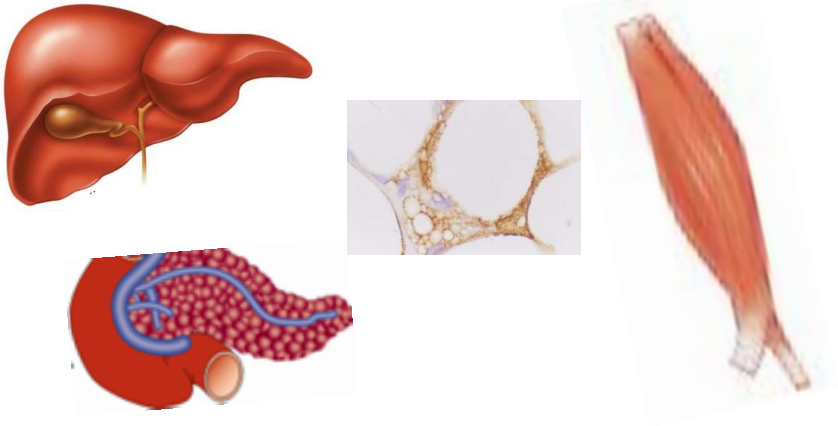


OVER REPLACEMENT



MANY STUDIES HAVE EVALUATED THE IMPACT OF HC ON METABOLIC AND BONE PROFILE & QOL, ANALYZING THE IMPACT OF DIFFERENT DOSES AND TIMING, FREQUENTLY COMPARING PATIENTS TREATED WITH HC AND CA (SHORT-ACTING THERAPIES) *VS* PREDNISONE AND DMX (LONG-ACTING THERAPIES)





METABOLIC SYNDROME

Visceral obesity
Dyslipidemia
IGT/ Diabetes mellitus
Arterial hypertension
Cardiovascular diseases

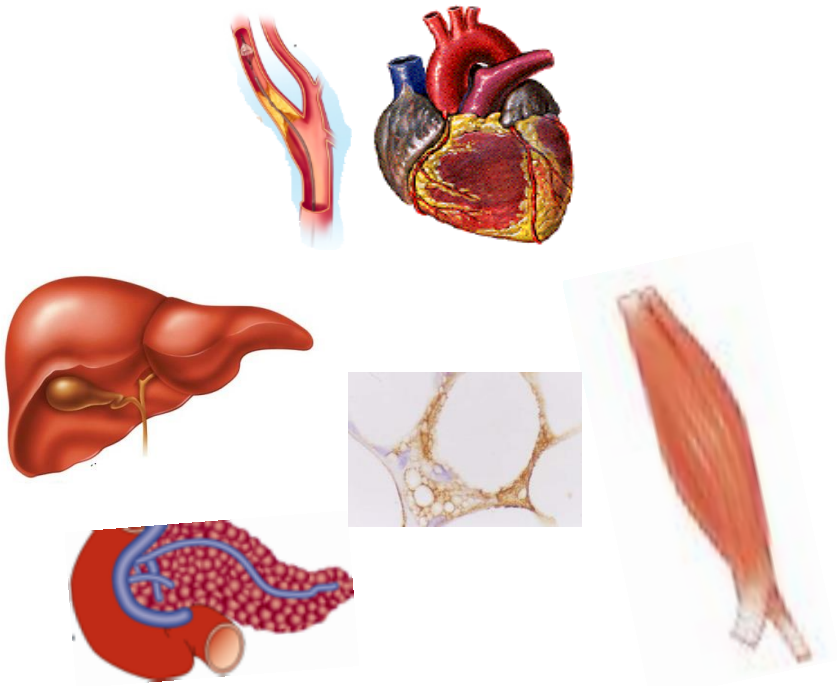
Impaired bone metabolism
Osteoporosis

Quality of Life

Psychological morbidity and QoL impairment

IGT: impaired glucose tolerance; QoL: quality of life

TREATMENT & METABOLIC SYNDROME



METABOLIC SYNDROME

Visceral obesity
Dyslipidemia
IGT/ Diabetes mellitus
Arterial hypertension
Cardiovascular diseases

- CURRENTLY USED GCS ARE KNOWN TO IMPAIR GLUCOSE TOLERANCE AND METABOLIC PARAMETERS LEADING TO AN INCREASED CARDIOVASCULAR RISK
- BOTH HIGHER TOTAL DAILY DOSE AND DELIVERY PATTERN MAY EXPLAIN THESE POOR OUTCOMES
- REDUCING TOTAL HC DOSES (<20MG/DAY) & AVOIDING CORTISOL OVER-EXPOSURE DURING EVENING AND NIGHT MAY RESULT IN A METABOLIC PROFILE IMPROVEMENT

Al-Shoumer K.A.S. et al. Clinical Endocrinology 1995; Danilowicz K. Et al. Pituitary 2008; Filipsson H et al. JCEM 2006; Plat L et al. JCEM 1999; McConnell E.M. et al. Clinical Endocrinology 2002

TREATMENT & BONE

- There is a paucity of data on the GC replacement effects on bone metabolism in SAI pts
- Currently used GCs are associated with poor bone metabolism
- Pts should be maintained on the lowest possible HC replacement doses
- Considering that alterations in cortisol rhythmcity may impair osteoblast function, circadian replacement cortisol therapy could positively impact on circadian bone turnover
- Long-term management of adverse bone effects:
  - Calcium (1000-1200 mg/day)
  - Vitamin D (>75 nmol/L)
  - GC dose: 0.2-0.3 mg/kg/day HC eq.
- Osteoporosis assessment: DEXA & spine X-ray if ospeopenic
- Fracture risk assessment tool (FRAX)

Impaired bone metabolism
Osteoporosis

DEXA: Dual-energy X-ray absorptiometry

Esteban NV. Et al JCEM 1991; Lee P. & Greenfield J. R. Clinical Endocrinology 2015; Peacey SR. Et al. Clinical endocrinology 1997; Behan L. A. et al. EJE 2014; Heshmati HM. Et al. JCEM 1998

TREATMENT & QoL

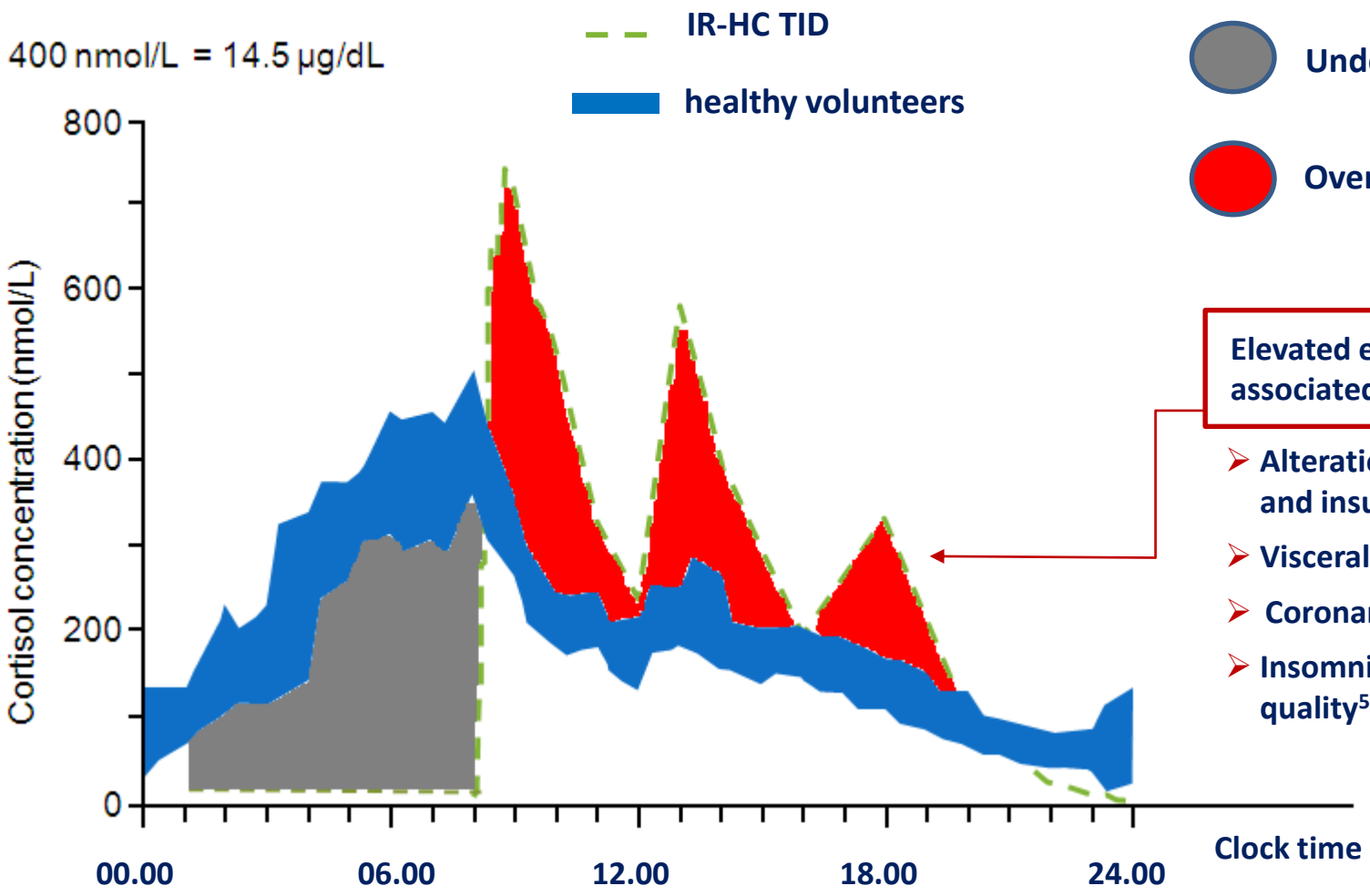
- CURRENT GC REPLACEMENT THERAPY WAS REPORTED TO HAVE A SIGNIFICANT IMPACT ON SUBJECTIVE PERCEIVED HEALTH OUTCOMES, NOT ABLE TO RESTORE QOL IN AI PTS
- SAI PTS REPORTED LESS SATISFACTION AND PERCEIVED THEIR QOL AS MORE IMPAIRED THAN PAI PTS
- HIGHER REPLACEMENT DOSES (>30 MG/DAY) APPEAR ASSOCIATED WITH A NEGATIVE EFFECT ON QOL
- TWICE-DAILY REGIMEN APPEARS SUPERIOR TO THRICE-DAILY REGIMEN
- HC AND CORTISONE ACETATE SHOULD BE PREFERRED TO PREDNISONE

Psychological morbidity and QoL impairment

Aulinas A. & Webb S.M. Expert Rev. Pharmacoecon. Outcomes Res. 2014; Forss M. Et al. BMC Endocrine Disorders 2012; Chapman SCE. Et al Clinical Endocrinology 2016; Bleicken B. Et al. Clinical Endocrinology 2010; Bleicken B. Et al. EJE 2008; Benson S. Et al. EJE 2012 ; Ragnarsson O. Et al. EJE 2014

CURRENT GCs IN AI PTS ARE NOT PHYSIOLOGICAL

HC TID (20 mg/day) was found to be the best regimen to reproduce physiological levels [1]



Elevated evening levels are associated with:

- Alterations in glucose tolerance and insulin sensitivity[2]
- Visceral obesity[3]
- Coronary artery calcification[4]
- Insomnia and reduced sleep quality[5-7]

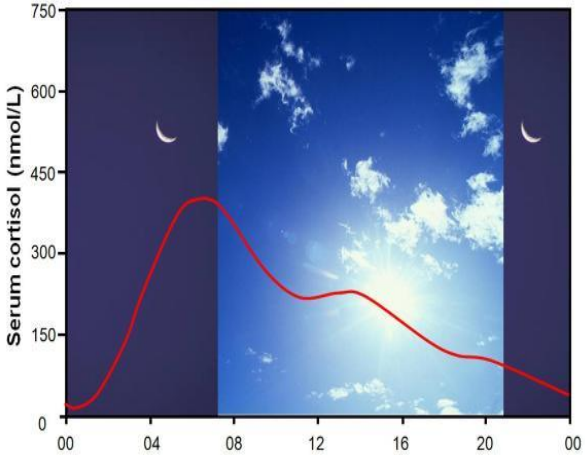
IR-HC TID: immediate release hydrocortisone thrice daily

1: Simon N. et al. Clin Pharmacok. 2010; 2. Plat L. et al. JCEM 1999; 3. Gangwisch JE. et al. Obes Rev. 2009; 4. Matthews KA et al. Psychosom. Med. 2006; 5. García-Borreguero D. et al. JCEM 2000; 6. Vgontzas AN et al. JCEM 2001; 7: Kumari M. et al JCEM 2009

THE CHALLENGE: RESTORING A NORMAL DAILY CORTISOL PROFILE

- 54 % 8 am
  44 % 4 pm
  32% 12 pm
  } OVER OR UNDER-TREATED [1]

- 34.6%: LOW ADHERENCE [2]
- 38% of pts reported multiple daily dosing to be an issue [3]



NEW MODIFIED-RELEASE HC FORMULATIONS SEEM TO BE STRONGLY NECESSARY

PRIMARY ADRENAL INSUFFICIENCY

1: Simon N. et al. Clin Pharmacok. 2010; 2: Chapman SCE. Et al Clinical Endocrinology 2016; 3: Forss M. Et al. BMC Endocrine Disorders 2012

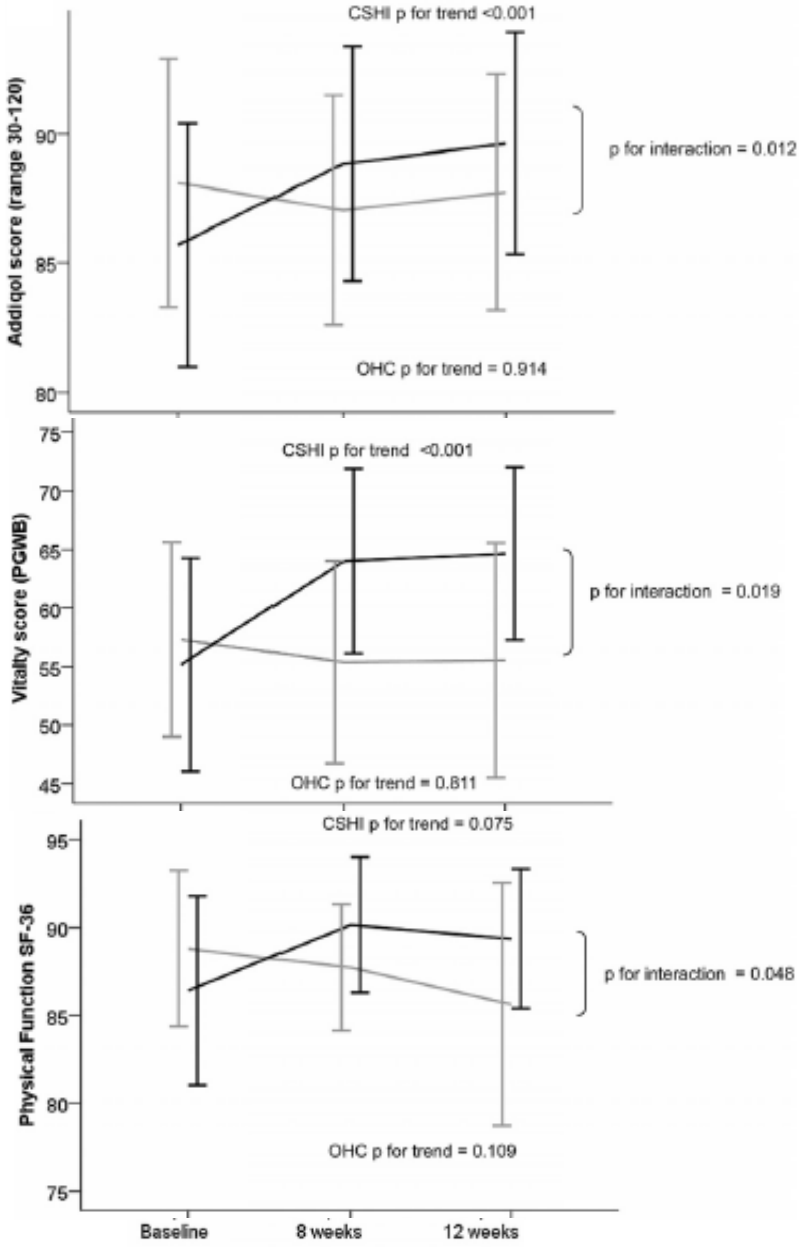
CONTINUOUS SUBCUTANEOUS HC INFUSIONS (CSHI)

- Multicenter, crossover, randomized clinical trial
- 33 PAI pts (48±12 ys; 25 F, 8M) 12 weeks
- CSHI vs TID IR-HC

CSHI produces a more physiological circadian cortisol rhythm than TID IR-HC and induce normalization of morning ACTH and cortisol levels

**FASTING GLUCOSE,
QOL, VITALITY SCORES,
SF36 PHYSICAL FUNCTION**

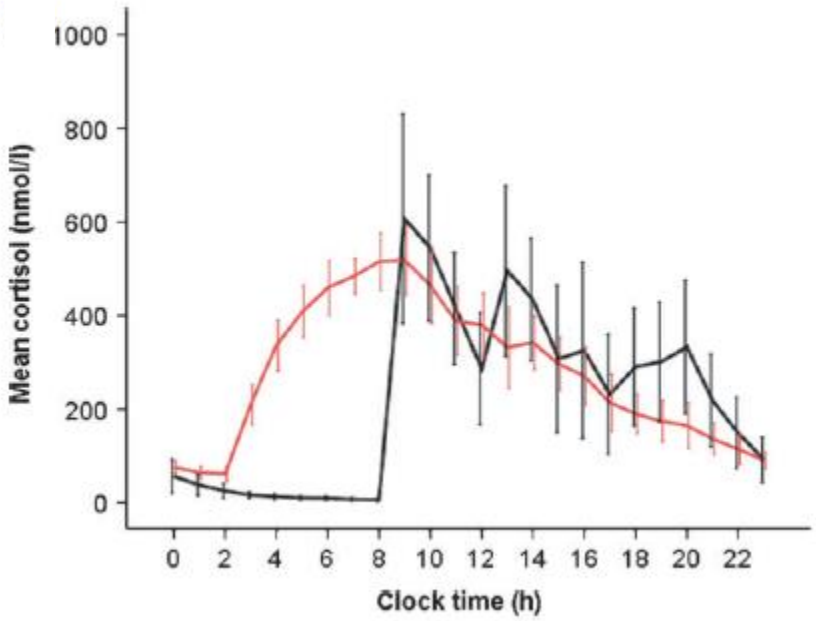
**WEIGHT, W/H RATIO, BP,
INSULIN, C PEPTIDE, HOMA-IR
LIPID PROFILE,
SLEEP**

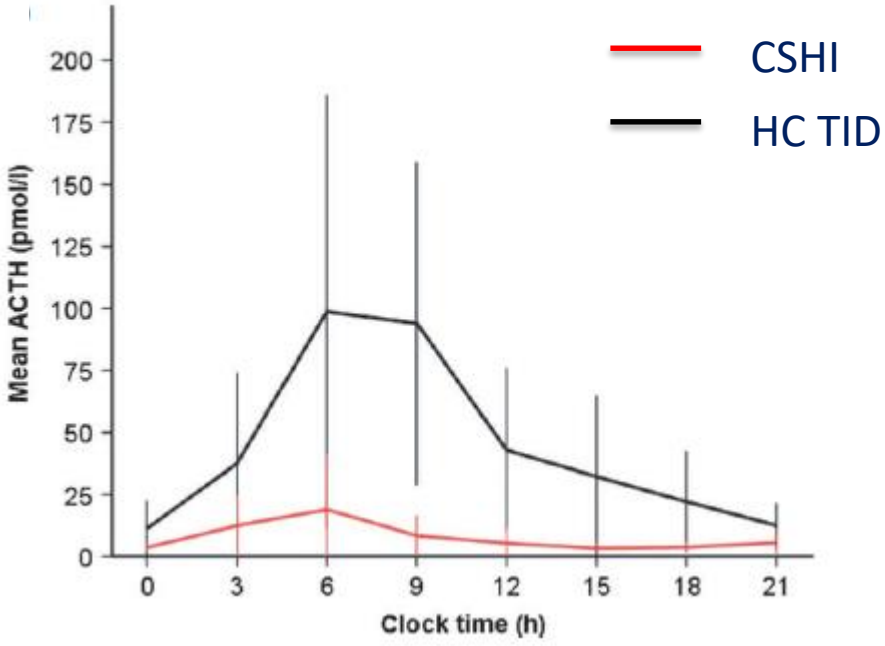


Øksnes M. et al. JCEM 2014

CONTINUOUS SUBCUTANEOUS HC INFUSIONS (CSHI)

- Open, randomized, two-period, 12- week crossover multicentre trial
- 10 Norwegian PAI pts (circadian group); 15 Swedish PAI pts (insulin clamp group)
- CSHI vs TID IR-HC





CSHI produces a more physiological circadian cortisol curve, including a late-night cortisol surge, avoiding the peaks and troughs seen with TID HC treatment, and induces ACTH levels nearly normal. The clinical significance of restoring the normal night-time cortisol surge in patients with AD might be important for achieving metabolic homoeostasis.

Bjrnsdottir S. et al. Clinical Endocrinology (2015)

CONTINUOUS SUBCUTANEOUS HC INFUSIONS (CSHI)

- Open, randomized, two-period, 12- week crossover multicentre trial
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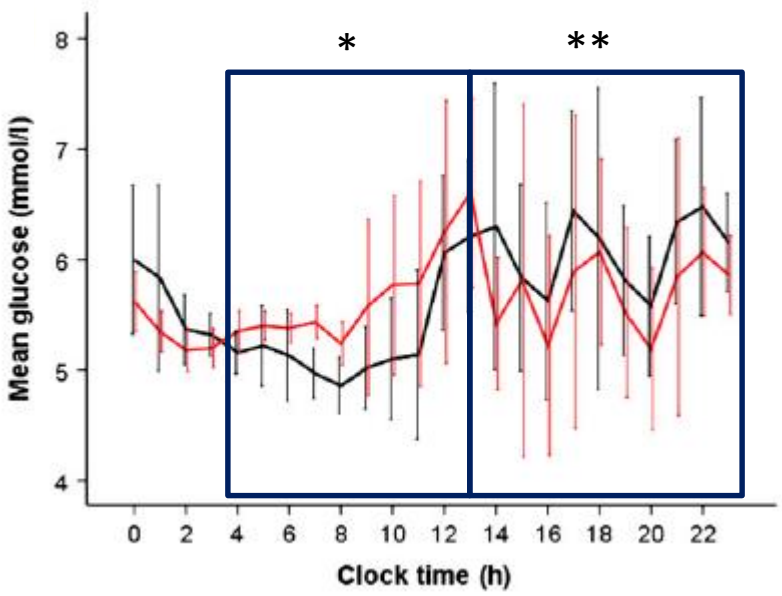
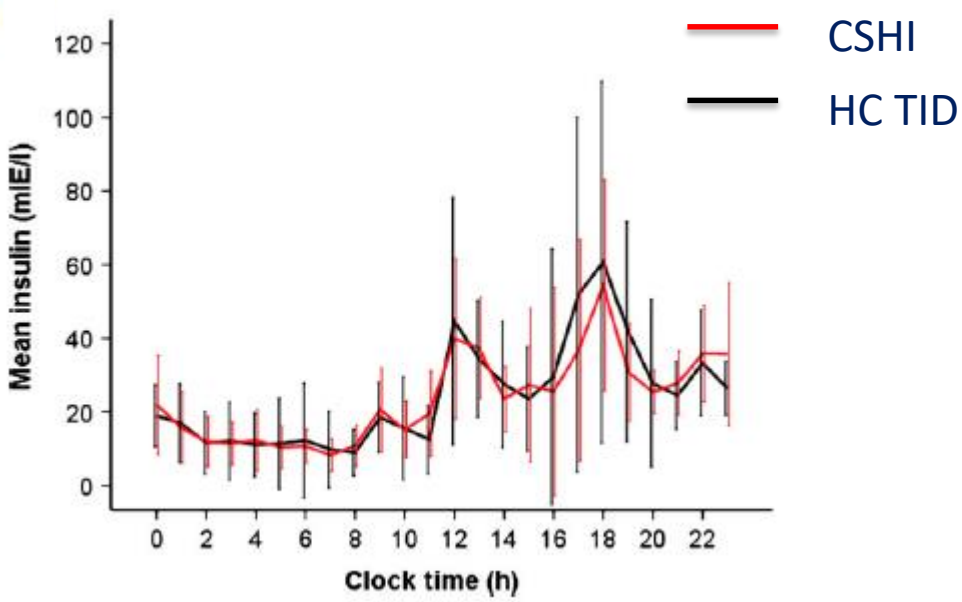




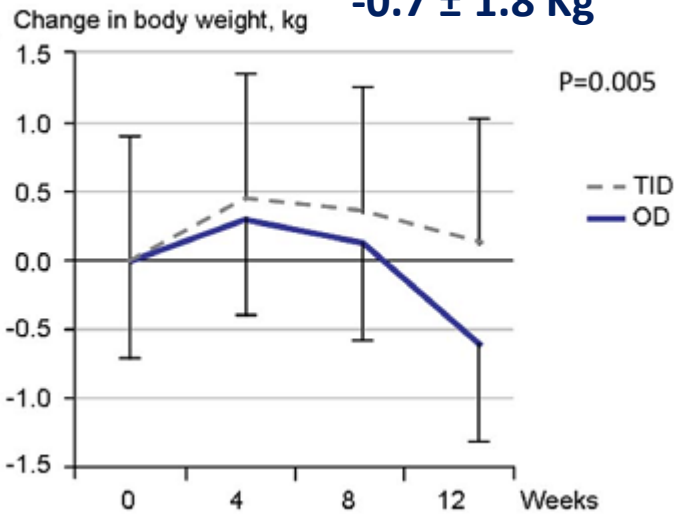
- CSHI prevented glucose decrease during the night and low morning glucose levels and might become a therapeutic option to diminish the risk of night-time hypoglycaemia, particularly in AD pts and concomitant insulin-treated diabetes mellitus*
- Elevated late afternoon and evening cortisol and glucose levels were avoided by CSHI, reducing the known deleterious metabolic effects**
- No difference in insulin sensitivity was observed between the two treatment arms

Bjrnsdottir S. et al. Clinical Endocrinology (2015)

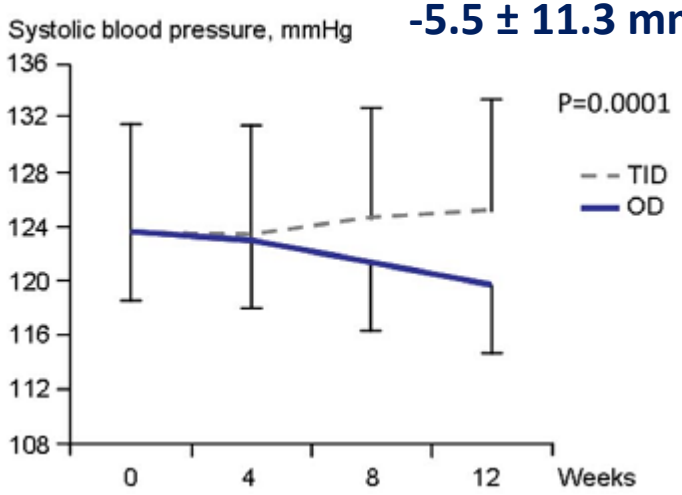
DUAL RELEASE-HC: DECREASE IN BODY WEIGHT, SBP, DBP, HbA1c

- Open, controlled, randomized, 12-wk crossover, multicenter trial
- 64 PAI patients ; 11 with Diabetes Mellitus
- DR-HC (30 mg/day) *vs* IR-HC TID tablets

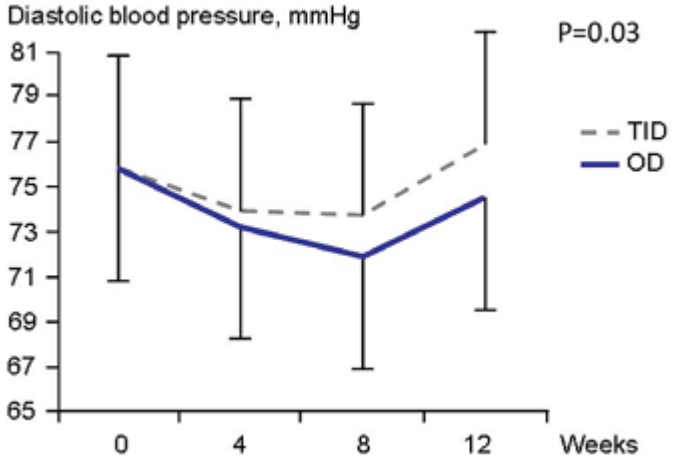
-0.7 ± 1.8 Kg



-5.5 ± 11.3 mmHg



-2.3 ± 8 mmHg

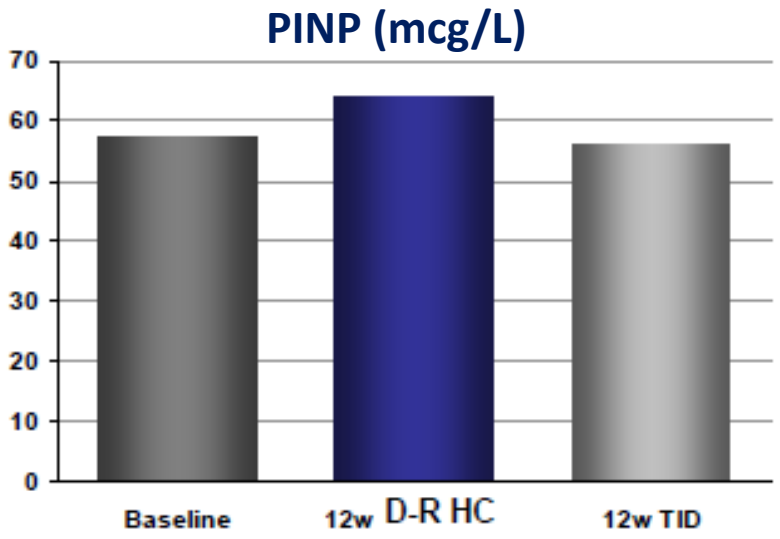


- **HbA1c:** -0.1 ± 0.4% (p =0.0006)
- **HbA1c in diabetic pts:** -0.6 ± 0.6% (p =0.0039)
- **HDL Chol:**-0.1 ± 0.2 mmol/L (p <0.0001)
- **Triglycerides:** 0.2 ± 0.6 mmol/L (p= 0.008)

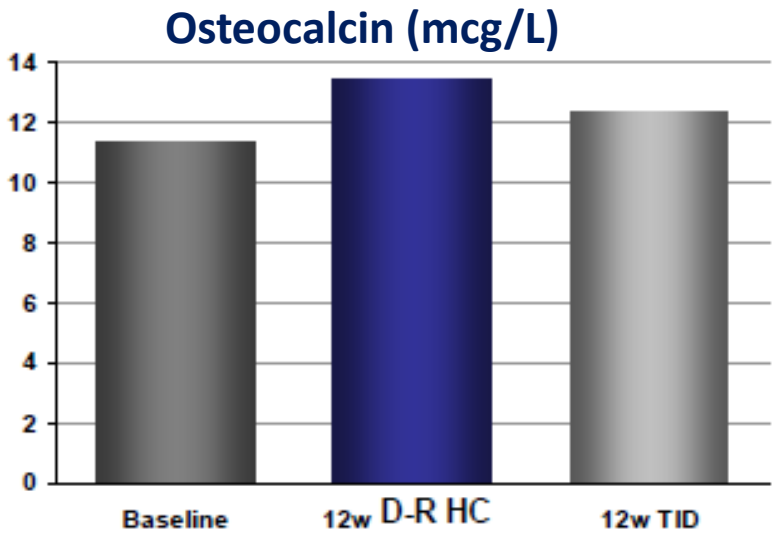
Johannsson G. et al. JCEM 2012

DUAL RELEASE-HC: IMPROVEMENTS IN BONE FORMATION BIOMARKERS

- Open, controlled, randomized, 12-wk crossover, multicenter trial
- 64 PAI patients ; 11 with Diabetes Mellitus
- DR-HC (30 mg/day) *vs* IR-HC TID tablets



DR-HC-TID: 6.1 ± 15.5 µg/L
P< 0.01



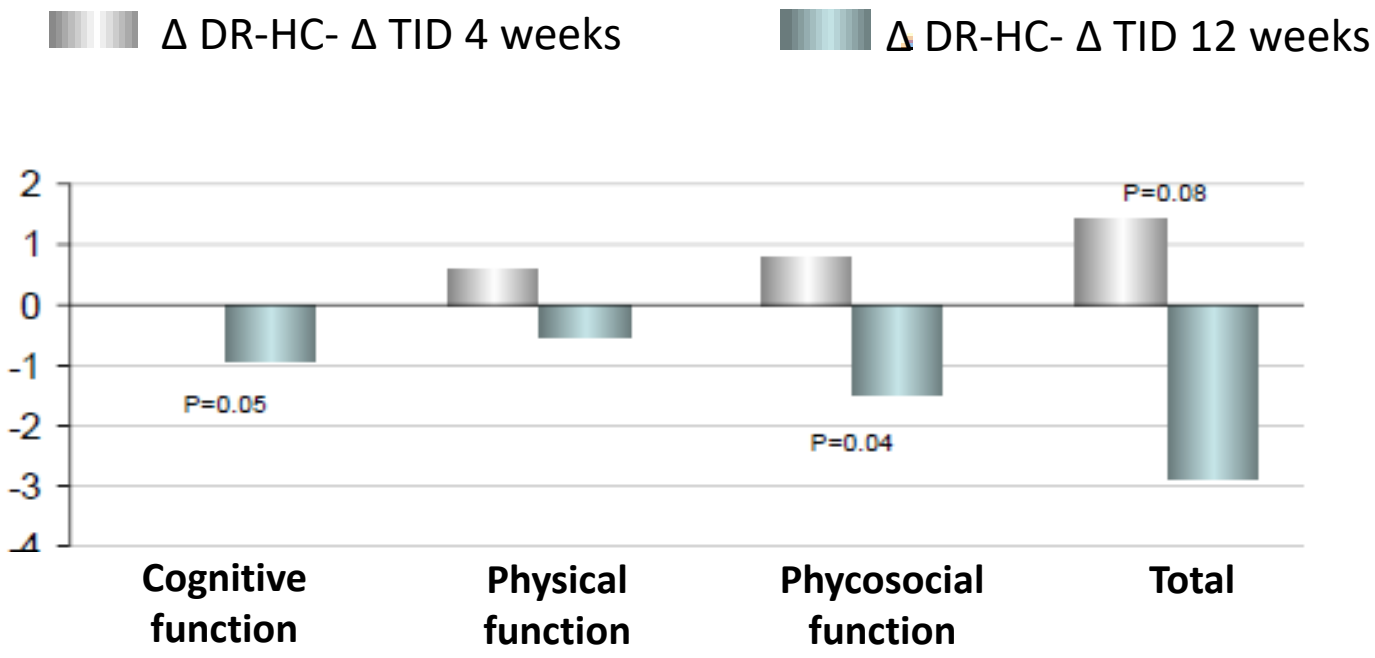
DR-HC- TID: 0.7 ± 4.5 µg/L
P< 0.2

PINP: procollagen type I N-propeptide

Figure adapted from: Johannsson G. et al. JCEM 2012

DUAL RELEASE-HC: IMPROVEMENTS IN QUALITY OF LIFE

- Open, controlled, randomized, 12-wk crossover, multicenter trial
- 64 PAI patients ; 11 with Diabetes Mellitus
- DR-HC (30 mg/day) *vs* IR-HC TID tablets

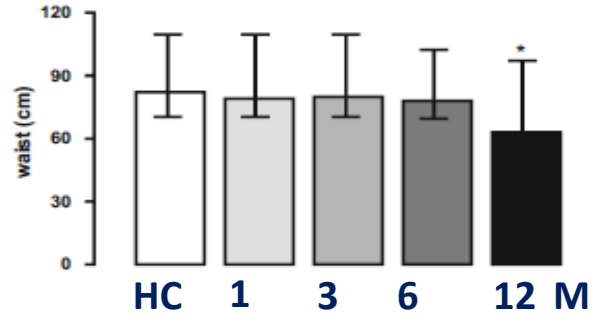


Johannsson G. et al. JCEM 2012

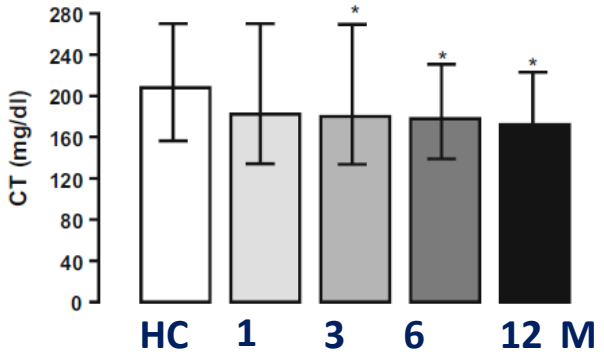
DUAL RELEASE-HC: DECREASE IN WC, HbA1c, TOTAL AND LDL CHOLESTEROL

- 19 PAI patients (47.3 ± 3.2 ys; 15F, 4M)
- 12 months
- DR-HC (20 mg/day) *vs* IR-HC TID tablets

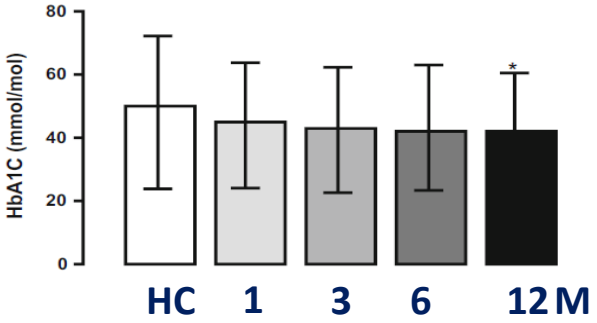
WAIST CIRCUMFERENCE (WC)



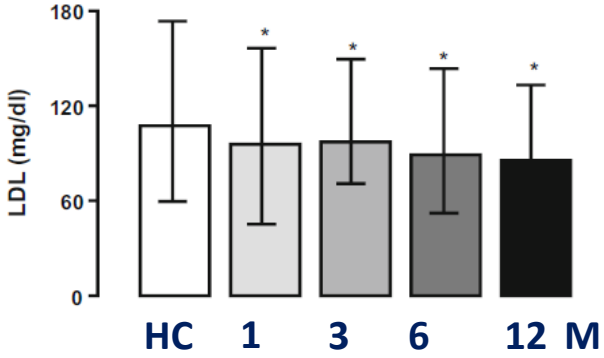
TOTAL CHOLESTEROL



HBA1C



LDL CHOLESTEROL



Giordano R. et al Endocrine 2015

DUAL RELEASE HC: DECREASE IN BMI, HbA1c AND CHOLESTEROL LEVELS

- 30 PTS: 15 PAI; 9 SAI; 6 CAH patients (23 F, 7 M)
- 3-12 months (234 ± 132 days)
- DR-HC *vs* IR-HC TID/PREDNISONE/DXM

Outcome	Baseline		Follow-up		
	No. of patients	Observed mean ± S.E.M.	No. of patients	Observed mean ± S.E.M.	Adjusted P change
BMI					
Modified release HC	30	26.0 ± 0.75	30	25.6 ± 0.71	0.006
Conventional HC	20	25.7 ± 1.14	20	25.8 ± 1.08	0.985
interaction[c]					
HbA1c					
Modified release HC	27	6.04 ± 0.29	28	5.86 ± 0.28	0.005
Conventional HC	20	5.63 ± 0.13	18	5.72 ± 0.15	0.807
interaction[c]					
Cholesterol					
Modified release HC	30	213.8 ± 7.97	29	200.1 ± 7.57	0.036
Conventional HC	19	221.8 ± 10.8	19	210.9 ± 13.1	0.320

Quinkler M. et al. EJE 2015

DUAL RELEASE HC: NO SIGNIFICANT DECREASE IN QOL SCORES vs SIGNIFICANT DECREASE IN CONVENTIONAL HC

- 30 PTS: 15 PAI; 9 SAI; 6 CAH patients (23 F, 7 M)
- 3-12 months (234 ± 132 days)
- DR-HC *vs* IR-HC TID/PREDNISONE/DXM

Outcome	Baseline		Follow-up		
	No. of patients	Observed mean ± S.E.M.	No. of patients	Observed mean ± S.E.M.	Adjusted P change
AddiQoL					
Modified release HC	30	83.8 ± 1.81	30	84.9 ± 1.95	0.629
Conventional HC	20	84.0 ± 2.11	20	80.9 ± 2.50	0.016
interaction[c]					
Fatigue					
Modified release HC	30	22.4 ± 0.68	30	22.6 ± 0.81	0.793
Conventional HC	20	21.1 ± 0.66	20	19.9 ± 0.85	0.024

Quinkler M. et al. EJE 2015

DUAL RELEASE HYDROCORTISONE LONG-TERM SAFETY

% OF DAYS OF INCREASED USE OF PLENADREN AND TID HC

	PLENADREN Percentage of days with increased hydrocortisone use (n=64) Mean Median (range)	TID Percentage of days with increased hydrocortisone use (n=64) Mean Median (range)
Increased hydrocortisone use due to intercurrent illness	**2.5%** 0.0 (0.0–25.0%)	**1.6%** 0.0 (0.0–23.8%)
Increased hydrocortisone use due to non-intercurrent illness e.g. physical or mental stress	**1.3%** 0.0 (0.0–27.4%)	**0.4%** 0.0 (0.0–6.0%)

No difference in additional dosing between Plenadren and TID HC

Johannsson G . et al. JCEM 2012; Nilsson AG. et al. EJE 2014

FREQUENCIES OF ADVERSE EVENTS (AE) AND SERIOUS AE (SAE)

		Randomised controlled phase II/III		Phase III open extension		Phase IIIb	
		0-3 months TID n=64	0-3 months PLENADREN n=64	3-6 months PLENADREN n=59	6-9months PLENADREN n=57	9-12 months PLENADREN n=55	12-15 months PLENADREN n=54
AEs	No. of AEs	75	103	37	50	49	46
	% patients	65.6%	73.4%	50.8%	54.4%	50.9%	51.9%
SAEs	No. of SAEs	2	6	2	4	2	2

Increase of AE/SAE in patients receiving new treatment with Plenadren is only transient within the first month

Johannsson G . et al. JCEM 2012; Nilsson AG. et al. EJE 2014

DUAL RELEASE HYDROCORTISONE: LONG-TERM SAFETY

- Open-label, multicenter study of DR-HC conducted at 5 university clinics in Sweden
- 70 PAI PTS
- 5-year extension
- Seventy patients reported 1060 AEs: 85% were considered unrelated to DR-HC
- Nasopharyngitis (70%), fatigue (52%) and gastroenteritis (48%)
- 4/65 SAE possibly related to DR-HC: acute AI (n = 2), gastritis (n = 1), syncope (n = 1)
- Two deaths: fall from height, subarachnoid hemorrhage, considered to be unrelated to DR-HC
- Intercurrent illness episodes remained relatively stable after the switch from conventional GCs to DR-HC

Nilsson AG. et al. EJE 2017

CONCLUSIONS

- **Secondary adrenal insufficiency patients require life-long GC treatments**
- **Conventional therapy, mostly based on HC *bid* or *tid,* is associated with life expectancy reduction, increased morbidity and impaired QoL, compared with general population**
- **Both increased exposure to cortisol and the non-physiological cortisol profile may contribute to these adverse outcomes**
- **Reducing total HC doses on the lowest possible & avoiding cortisol over-exposure during evening and night may result in a metabolic, bone profile and QoL improvement**
- **The failure of conventional treatment regimens to restore full health in adrenal insufficiency pts warrants consideration of alternative methods of GC replacement**
- **New treatments, HC infusions and Dual release HC formulations, that minimize daily GC exposure and aim to achieve physiological cortisol replacement are developing, representing an important step in adrenal insufficiency management**
- **These formulations have been demonstrated able to induce a significant improvement in the metabolic profile, body composition, bone metabolism, QoL and treatment compliance**
- **Long-term studies, mainly focused on SAI pts, are needed to confirm and extend these data**

THANKS

Dipartimento di Medicina Clinica e Chirurgia,
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