PROPOSAL:
Study on the effect of the shift from classic glucocorticoid (GC) replacement therapy (CGR-T) to dual-release hydrocortisone replacement therapy (DRHC-T) on bone turnover, bone mineral density and bone quality in patients with Addison disease

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THE EFFECTS OF CLASSIC GC REPLACEMENT THERAPY ON BONE

Effect of Glucocorticoid Replacement Therapy on Bone Mineral Density in Patients with Addison Disease

Peter M.J. Zelissen, MD; Ronald J.M. Croughs, MD; Peter P. van Rijk, MD; and Janthony A. Raymakers, MD

Ann Intern Med. 1994;120:207-210

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. 2012;97:85-92

Low-dose hydrocortisone replacement therapy is associated with improved bone remodelling balance in hypopituitary male patients

Lucy-Ann Behan[1], Grainne Kelleher[2], Mark J Hannon[1], Jennifer J Brady[3], Bairbre Rogers[1], William Tormey[2], D Smith[1], Christopher J Thompson[1], Malachi J McKenna[3,4] and Amar Agha[1]

Eur J Endocrinol. 2014; 170;141–150

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AIM

- **Effect of the shift from CGR-T to DRHC-T in patients with Addison disease on bone turnover, bone mineral density, bone quality and incident vertebral fractures**

DESIGN

- **Prospective randomized study**
- **Inclusion Criteria: eugonadal patients, age 20-50 years, with Addison Disease, BMI 19-30 kg/m^2, treated with cortisone acetate or hydrocortisone with good clinical and metabolic control.**
- **Exclusion Criteria: hyperthyroidism, not controlled hypothyroidism, hypoparathyroidism, hypercalciuria, type 1 diabetes, rheumatic diseases, chronic inflammatory bowel diseases, coeliac disease, renal and/or liver diseases, drugs influencing bone, history of severe hypovitaminosis D**
- **Sample size: Prior data** *(Behan LA et al, EJE 2014)* **suggest that the difference in the response of matched pairs is about 30% (30%SD). We will need to study 13 pairs of subjects to be able to reject the null hypothesis that this response difference is zero with probability (power) 0.9 and Type I error 0.05.**

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Subjects

- 60 consecutive patients will be randomized to
- Continue cortisone acetate therapy (Group A, n=15)
- Continue hydrocortisone therapy (Group B, n=15)
- Shift from cortisone acetate to DRHC-T (Group C, n=15)
- Shift from hydrocortisone to DRHC-T (Group D, n=15)
- 30 age-BMI-gender matched controls
- At enrolment two oral bolus of cholecalciferol 100.000 U (every 15 day) will be given to all subjects, and patients with an estimate calcium intake below 500 mg/day will be supplemented with calcium carbonate 500 mg/day
- The study begins 15 days after the second cholecalciferol supplementation

Methods

Baseline and at 6, 12 and 18 months

- Electrolytes, aldosterone, renin, bone alkaline phosphatase (bALP), albumin-adjusted calcium (aCa), phosphate (P), parathyroid hormone (PTH), 25 hydroxyvitamin D (25OHD), N-terminal propeptide of type 1 collagen (PINP), osteocalcin (OC), C-terminal telopeptide of type 1 collagen (CTX), β-catenin, sclerostin (SS), dickkopf-related protein 1 (Dkk1)
- 24 h urinary calcium excretion, creatinine clearance, 3h morning fasting urinary phosphate, calcium and creatinine

Baseline and after 18 months

- BMD spine and femur, TBS, spinal X-ray

After 1 and 3 months since baseline

- OC, CTX, PINP, β-catenin, SS, Dkk1

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Expected Results:

Patients shifting from CGR-T to DRHC-T could have

- **Increase in bone turnover markers (OC and bALP>CTX)**
- **Increase in β-catenin levels and decrease in SS and Dkk-1 levels**
- **Increase or no decrease of TBS and, possibly, of BMD levels**
- **No increase of incident vertebral fractures**

State of the art and transferability:

- **Previous data suggest that low dose CGR-T is not associated with a BMD decrease. However, the GC-related fracture risk is largely independent of BMD. Reduced bone quality (indirectly measured by TBS) may account for this BMD-independent increase fracture risk.**
- **Previous data also suggest that low dose GCR-T improves bone remodelling. However, low dose CGR-T is often hardly obtainable in the majority of patients.**
- **The study could demonstrate that DRHC-T improves bone turnover and bone quality and that it may have a positive effect on bone by activating the osteoblast signaling.**
- **Therefore, if this hypothesis will be confirmed, the fracture risk profile should be included among the criteria for addressing the GC therapy of choice in patients with Addison disease.**

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

PAI	Women total	Premenopausal women	Postmenopausal women	Men
n	58	18	40	28
Age (yr)	57.6 ± 14.7	40.2 ± 6.8	65.5 ± 9.6[a]	51.6 ± 15.1[b]
Height (cm)	163.3 ± 6.6	166.2 ± 7.9	162.0 ± 5.5	177.6 ± 10.1
Duration of disease (yr)	17.8 ± 11.6	13.4 ± 8.4	19.5 ± 12.2	11.1 ± 9.5[b]
BMI (kg/m^2)	26.0 ± 4.4	24.5 ± 3.7	26.7 ± 4.5	25.9 ± 3.8
Daily HC-equivalent dose (mg)	20.9 ± 4.2	21.1 ± 4.3	20.9 ± 4.2	24.2 ± 5.81[b]
GC-dose per body surface (mg/m^2)	11.9 ± 2.6	12.1 ± 2.5	11.9 ± 2.7	12.2 ± 3.0
GC-packyears (g)	136.5 ± 94.4	100.3 ± 67.3	150.9 ± 99.8	95.5 ± 79.3
T-score femoral neck	−0.82 ± 1.3	0.06 ± 0.8	−1.24 ± 1.2	−0.81 ± 1.14
T-score Ward's triangle	−1.43 ± 1.4	−0.38 ± 0.9	−1.96 ± 1.3	−1.4 ± 1.43
T-score lumbar spine (L1–L4)	−0.98 ± 1.4	−0.19 ± 1.1	−1.36 ± 1.3	−0.71 ± 1.7
Z-score femoral neck	0.07 ± 0.92	0.24 ± 0.73	−0.01 ± 0.99	−0.23 ± 1.06
Z-score Ward's triangle	−0.24 ± 0.9	−0.04 ± 0.89	−0.34 ± 0.89	−0.49 ± 1.24
Z-score lumbar spine (L1–L4)	−0.19 ± 1.1	−0.18 ± 1.1	−0.19 ± 1.1	−0.6 ± 1.6
Reported fractures after age of 50 yr	13/40 (32.5%)	0/1 (0%)	13/39 (33.3%)	2/17 (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%)

Adult patients with primary adrenal insufficiency and congenital adrenal hyperplasia on low glucocorticoid doses showed normal BMD within the normal reference range.

The use of longer acting prednisolone resulted in significantly lower BMD in patients with primary adrenal insufficiency.

K. R. Koetz et al, J Clin Endocrinol Metab 2012

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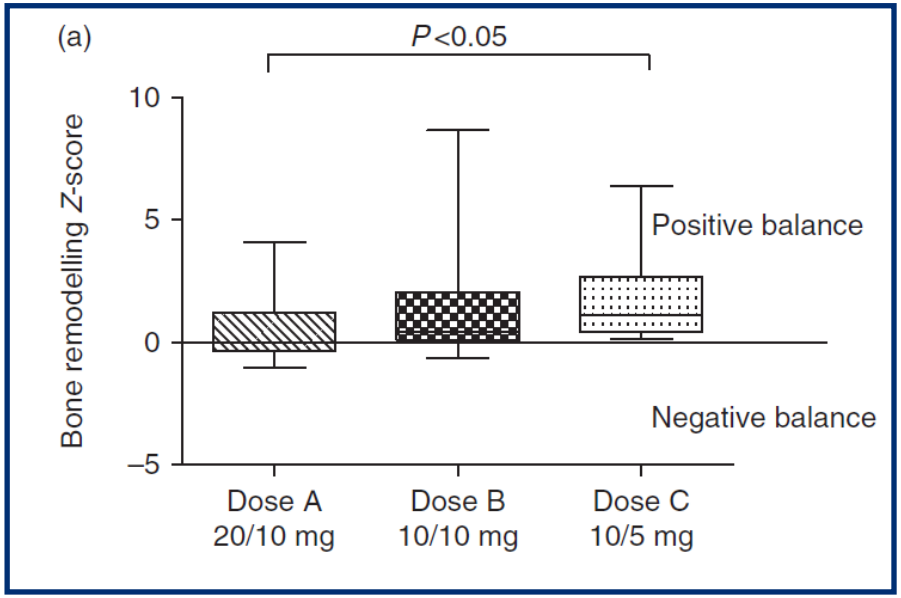

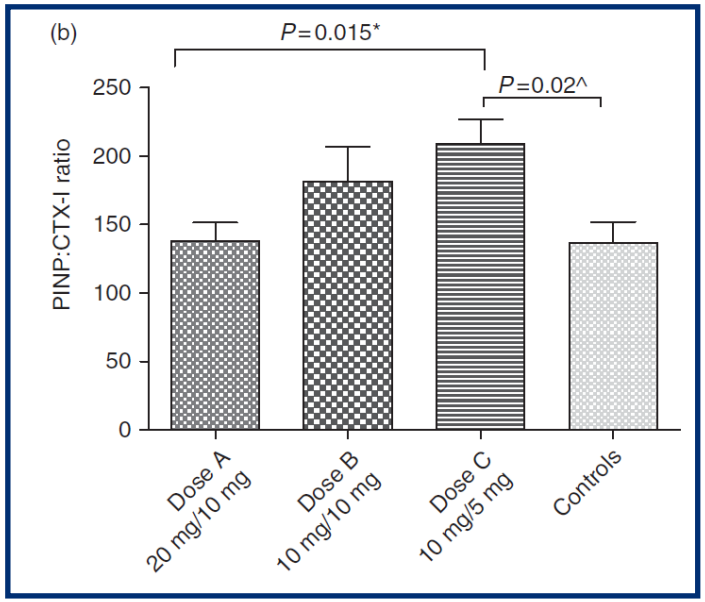

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Table 1. Characteristics of Patients with Addison Disease Who Had either Normal or Decreased Bone Mineral Density*

Variable	Men		*P* Value	Women	
	Normal BMD	Decreased BMD		Normal BMD	Decreased BMD
Patients, *n*	21	10		56	4
Mean (±SD) age, *y*	41.0 ± 13.6	45.1 ± 15.7	0.49	46.6 ± 13.9	50.0 ± 14.3
Duration of substitution, *y*	10.9 ± 9.2	11.0 ± 10.1	0.99	10.6 ± 8.5	7.3 ± 3.8
BMI, kg/m^2	25.3 ± 3.5	23.5 ± 3.3	0.17	24.8 ± 3.5	27.0 ± 4.4
Postmenopausal, *n* (%)†	NA	NA	NA	11 (19.6)	3 (75)
Hydrocortisone dose, *mg/d*	28.4 ± 7.3	31.0 ± 6.3	0.32	28.6 ± 7.0	26.8 ± 5.4
Hydrocortisone dose/kg body weight, *mg/kg per day*	0.35 ± 0.10	0.43 ± 0.08	0.032	0.43 ± 0.13	0.37 ± 0.11
Adrenocorticotropin, *pmol/L*	44 ± 11	27 ± 13	0.32	34 ± 9	12 ± 6
Testosterone, *nmol/L*	17.5 ± 9.4	17.5 ± 5.9	0.99	0.32 ± 0.31	0.19 ± 0.21
Androstenedione, *nmol/L*	1.17 ± 0.65	0.96 ± 0.56	0.36	0.93 ± 1.03	0.57 ± 0.71
DHEA-S, *μmol/L*	0.90 ± 0.52	0.86 ± 0.41	0.81	0.22 ± 0.82	0.11 ± 0.08
Estradiol, *pmol/L*	NA	NA	NA	219 ± 330	84 ± 58
Bone mineral density, gBA/cm^2					
Lumbar spine	1.13 ± 0.19	0.81 ± 0.08		1.02 ± 0.15	0.77 ± 0.20
Left femoral neck	0.86 ± 0.17	0.66 ± 0.10		0.75 ± 0.10	0.57 ± 0.10
Right femoral neck	0.86 ± 0.17	0.65 ± 0.09		0.75 ± 0.11	0.59 ± 0.08

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- **bone turnover**
- **bone mineral density**
- **bone quality**

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Methods

Anamnesi personale e familiare e questionari su cadute e consumo di calcio.

Baseline e dopo 6, 12 e 18 mesi:

- emocromo, uricemia, transaminasi, elettroliti, colesterolo totale, trigliceridi, colesterolo-HDL, colesterolo-LDL,
- glicemia basale a digiuno, emoglobina glicata, insulina, C-peptide,
- fosfatasi alcalina e isoenzima osseo della ALP (bALP), calcio corretto per albumina, fosforo, paratormone, 25OHvitaminaD, propeptide N-terminale del collagene di tipo I, osteocalcina (OC) , telopeptide C-terminale del collagene di tipo I (CTX), WNT, β-catenina, sclerostina, dickkopf-related protein 1 (Dkk1), glucagon-like peptide 1 (GLP1), glucagon-like peptide 2 (GLP2), glucose-dependent insulinotropic polypeptide (GIP)
- esame delle urine, microalbuminuria, calciuria 24 ore, clearance creatinina, calcio,
- fosforo (P) e creatinina (Cr) nella seconda minzione del mattino

Baseline and o 18 mesi

- proteine totali, elettroforesi siero-proteica
- BMD spine and femur, TBS

Dopo 15, 45, 180, 365, giorni dall'arruolamento

OC, CTX, WNT, β-catenina, sclerostina, Dkk1, GLP1, GLP2 e GIP

Baseline e 24 mesi

Rx laterale dorso-lombare (T4-L4) per morfometria vertebrale.

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