References of Consensus 4 on Cortisol Replacement Therapy in Milder Forms of Adrenal Deficiency in Adults

I) CORTISOL IS ESSENTIAL FOR SURVIVAL OF SEVERELY CORTISOL DEPLETED PATIENTS, AND FOR THE MENTAL AND PHYSICAL HEALTH OF ALL ADULTS

1. Cortisol is important for psychic well-being

Quality of life and fatigue: the association with lower cortisol levels

46. Tsopanakis C, Tsopanakis A. Stress hormonal factors, fatigue, and antioxidant responses to prolonged speed driving. Pharmacol Biochem Behav. 1998 Jul;60(3):747-51


Lower quality of life and fatigue: the improvement with cortisol or other glucocorticoid treatments


Depression lower glucocorticoid receptor levels and a circadian rhythm with lower fluctuations of serum cortisol


Depression: the improvement with cortisol or other glucocorticoid treatments


Anxiety: the association with lower cortisol levels or a flatter cortisol circadian rhythm


Anxiety: the improvement with cortisol or other glucocorticoid treatment


**Memory improvement for stressful events or avoidance reactions with glucocorticoid treatment**


**Anecdotal report on dementia reversed with glucocorticoid treatment**


**Sleep disorder: the association with cortisol levels**


2. *Cortisol is important for optimal body appearance*

**Hirsutism: the improvement with glucocorticoid treatment**


**Skin disorders: the improvement with glucocorticoid treatment**


3. *Cortisol may oppose age-related diseases*

**Hypercholesterolemia: the improvement with glucocorticoid treatment**

96. Boers M, Nurmohamed MT, Doelman CJ, Lard LR, Verhoeven AC, Voskuyl AE, Huizinga TW, van de Stadt RJ, Dijkmans BA, van der Linden S. Influence of glucocorticoids and disease activity on total and high density lipoprotein cholesterol in patients with rheumatoid arthritis. Ann Rheum Dis. 2003 Sep;62(9):842-5. *(glucocorticoids increase mildly the total cholesterol, but considerably more the HDL cholesterol, significantly lowering the atherogenic index)*

**Hyperhomocystinemia: the improvement with glucocorticoid treatment**


**Heart disease: the improvement with glucocorticoid treatment**

Diabetes – glucose intolerance: the improvement with glucocorticoid treatment in patients with inflammatory disease


Diabetes – glucose intolerance: the improvement of eye pathologies with glucocorticoid treatment


Rheumatism: the association with lower serum cortisol levels


Rheumatism: the improvement with cortisol or other glucocorticoid treatments


Bone density in rheumatoid disease: Reduced loss with glucocorticoid treatment

Neurodegenerative diseases: the improvement with glucocorticoid treatment


122. Moreira MA, Lana-Peixoto MA, Callegaro D, Haussen SR, Gama PD, Gabbai AA, Rocha FC, Lino AM; The BCTRIMS expanded consensus on treatment of multiple sclerosis: II. The evidences for the use of glucocorticoids and immunomodulatory treatments. Arq Neuropsiquiatr. 2002 Sep;60(3-B):875-80


Cancer: the improvement with glucocorticoids


Cancer: palliative help from glucocorticoid treatment


4. Cortisol is necessary for life:

Lifespan: the association with cortisol levels


Lifespan: the improvement with cortisol or other glucocorticoid treatments


II) TOOLS FOR DIAGNOSIS OF CORTISOL DEFICIENCY

1) Clinical cortisol evaluation


2) Serum cortisol tests

**Serum cortisol**


**Serum transcortin (Corticosteroid-binding globulin or CBG)**


**Serum ACTH- and CRF-stimulation tests**


3) Salivary cortisol


4) 24-hour urine cortisol tests

**Urinary cortisol and 17-OH-steroids**


161. Kobberling J, Von ZUT Mu1hen A. The circadian rhythm of free cortisol determined by urine sampling at two-hour intervals in normal subjects and in patients with severe obesity or Cushing's syndrome. J Clin Endocrinol Metab. 1974;38:313-19


188. Ely RS, Done AK, Ainger LE, Seely JR, Done AK, Kelley VC. Studies of 17-hydroxycorticosteroids. X. Urinary excretion of 17-hydroxycorticosteroids in patients with rheumatic fever. J Clin Endocrinol Metab. 1955;523-37


193. Sutherland DJA, Ruse JI, Laidlaw JC. Hypertension, increased aldosterone secretion, and low plasma renin activity relieved by dexamethasone. Can Med Assoc J 1966; 95:1109-19


III) GLUCOCORTICOID TREATMENT

1) Glucocorticoid medications

Oral Hydrocortisone


Oral glucocorticoid derivatives (prednisolone, methylprednisolone, dexamethasone, ...)


Inhaled glucocorticoids

212. Lipworth BJ. Systemic adverse effects of inhaled corticosteroid therapy: A systematic review and meta-analysis. Arch Intern Med. 1999 May 10;159(9):941-55

**Intranasal glucocorticoids**

213. Edwards TB. Effectiveness and safety of beclomethasone dipropionate, an intranasal corticosteroid, in the treatment of patients with allergic rhinitis. Clin Ther. 1995 Nov-Dec;17(6):1032-41 (“Despite the fact that topical nasal corticosteroids such as beclomethasone dipropionate are responsible for important improvements in the treatment of both allergic and nonallergic rhinitis as well as nasal polyposis and chronic sinusitis, these drugs may be underused, particularly in the pediatric population”)

2) Glucocorticoid treatment: dosage


219. Lipworth BJ. Systemic adverse effects of inhaled corticosteroid therapy: A systematic review and meta-analysis. Arch Intern Med. 1999 May 10;159(9):941-55 (“Marked adrenal suppression occurs with high doses of inhaled corticosteroid above 1.5 mg/d (0.75 mg/d for fluticasone propionate), although there is a considerable degree of interindividual susceptibility”)

Efficacy of low doses of glucocorticoids is greater than high doses

220. Williamson DR, Lapointe M. The hypothalamic-pituitary-adrenal axis and low-dose glucocorticoids in the treatment of septic shock. Pharmacotherapy. 2003 Apr;23(4):514-25 (“Although high-dose glucocorticoids have not positively affected clinical outcome, small trials in which low-dose glucocorticoids were administered to patients with septic shock and relative adrenal insufficiency have shown decreased mortality”)


3. Frequency of glucocorticoid treatment use


4. Importance to add anabolic hormone supplementation to glucocorticoid treatment: to assure a good anabolic-DHEA or other / catabolic-cortisol balance: for more information read the references on association of other hormones in one of the following sections on cortisol and bone density


5. Glucocorticoid treatment: interferences


6. Glucocorticoid treatment: safety, side effects, complications

Relative safety of low doses of glucocorticoids

228. da Silva JA, Jacobs JW, Kirwan JR, Boers M, Saag KG, Ines LB, de Koning EJ, Buttgerfeit F, Cutolo M, Capell H, Rau R, Bijlsma JW. Low-dose glucocorticoid therapy in rheumatoid arthritis. A review on safety: published evidence and prospective trial data. Ann Rheum Dis. 2005 Published Online First: 17 August 2005 (".. in the available literature on low-dose glucocorticoid therapy very little of the commonly held beliefs about the incidence, prevalence and impact (of adverse effects) of glucocorticoids proved to be supported by clear scientific evidence. … randomised controlled clinical trials … showed that the incidence, severity and impact of adverse effects of low dose glucocorticoid therapy in rheumatoid arthritis trials are modest, and often not statistically different to those of placebo. Conclusions: Probably many of the well known adverse effects of glucocorticoids are predominantly associated with high dose treatment.")

229. Strand V, Simon LS. Low dose glucocorticoids in early rheumatoid arthritis. Clin Exp Rheumatol. 2003 Sep-Oct;21(5 Suppl 31):S186-90 ("low dose glucocorticoid therapy (e.g. < or = 5 mg prednisone per day")


231. Glenn Haugeberg, MD, PhD; Anders Strand; Tore K. Kvien, MD, PhD; John R. Kirwan, MD Reduced Loss of Hand Bone Density With Prednisolone in Early Rheumatoid Arthritis. Results From a Randomized Placebo-Controlled Trial. Arch Intern Med. 2005;165:1293-7

Aggravation of salt loss, correctable by addition of fludrocortisone


Allergy reactions due to the excipients in drugs (succinate salt, sulphites, carboxy-methyl-cellulose, ..)


Adverse effects of higher doses of glucocorticoids


7. Glucocorticoid treatment: follow-up


4) SCREENING for PROBLEMS that MAY OCCUR with the USE of PHYSIOLOGICAL DOSES of GLUCOCORTICOIDS:

I) Can cortisol or glucocorticoid treatment suppress the secretion of hormones by the adrenal cortex?

Glucocorticoid treatments: may inhibit or even suppress the cortisol production by the adrenal glands depending upon the dose
1. **Subreplacement doses**

Very low hydrocortisone – **5 to 15 mg per day** – do not reduce the pituitary-adrenal axis, even not in CFS patients who are more sensitive to such a suppression. Insulin stress tests do not show any degree of suppression of endogenous adrenal function (ACTH or cortisol) with 5 to 10 mg per day of hydrocortisone.


2. Cleare AJ, Heap E, Malhi GS, Wessely S, O’Keane V, Miell J. Low-dose hydrocortisone in chronic fatigue syndrome: a randomised crossover trial. Lancet. 1999 Feb 6;353(9151):455-8 (double blind placebo study with low-dose (5 mg or 10 mg daily) hydrocortisone or placebo for 1 month; “Insulin stress tests showed that endogenous adrenal function was not suppressed by hydrocortisone”)

On the contrary, an **increased adrenal responsiveness to CRH stimulation in patients has been shown under this low dose of hydrocortisone**


**Low hydrocortisone - from 20 mg /day** of hydrocortisone to a maximum of 40- 60 mg/day depending on the degree of cortisol deficiency: at these doses a significant, but partial, moderate and temporary suppression of adrenal cortisol secretion occurs.


Normal low hydrocortisone – **25 to 35 mg per day**: leads to a 20 to 35 % decrease in endogenous ACTH and cortisol production in chronic fatigue patients, who have an enhanced negative feedback on the pituitary level. After stopping, it may take several days to several weeks to recover the previous adrenocortical status.


5 mg/day of prednisone inhibit in general only during the first 12 hours the cortisol production with the only consistent inhibition (41 to 47 %) 9 hours after of intake

7. Jerjes WK, Cleare AJ, Wood PJ, Taylor NF. Assessment of subtle changes in glucocorticoid negative feedback using prednisolone: Comparison of salivary free cortisol and urinary cortisol metabolites as endpoints. Clin Chim Acta. 2006 Feb;364(1-2):279-86 (“Prednisone at midnight (0h) caused a partial inhibition of urine cortisol metabolites that began at 0600 and ceased after 1800; Suppression of salivary cortisol was only consistently seen at 0900: mean suppression was 41+/-5% in males and 47+/-9% in females”)

Use of exogenous synthetic glucocorticoids by inhalation reduces the 30 minutes post-awakening cortisol levels (mildly for inhaled use, up to -60 % for systemic use at high doses, but no inhibitory effect on cortisol levels 12 h after.


2. **Total replacement doses**: 40 -60 mg per day ; suppress more, but not totally, adrenal cortisol secretion.

3) **Suprareplacement or supraphysiological doses**: more than 15 mg per day of oral prednisone (= 60 mg/day or more of oral hydrocortisone) are above the physiological range. It takes 5 days to 12 months to fully recover the initial adrenal axis depending upon the dose and the length of use of the overdose. Any person who
injections can restimulate and activate the adrenal cortex, accelerating adrenal recovery.

Recovery from adrenal suppression with ACTH-depot injections


Suprareplacement/pharmacological doses in severe critical illnesses

5. Hermus AR, Zelissens PM. Diagnosis and therapy of patients with adrenocortical insufficiency. Ned Tijdschr Geneeskd 1998 Apr 25;142(17):944-9 (Patients with primary adrenocortical insufficiency need substitution not only with glucocorticoids but also with mineralcorticoids. When pharmacological amounts of glucocorticoids (> 7.5 mg prednisone daily) are used for 3 weeks or longer, a clinically relevant suppression of the pituitary-adrenal axis is possible, and this may persist for one year after discontinuing the use of glucocorticoids)

Pharmacological doses are doses above 7.5 mg/day of prednisone


Recovery from adrenal suppression with ACTH-depot injections: In case of adrenal suppression, ACTH injections can restimulate and activate the adrenal cortex, accelerating adrenal recovery.


2. Can treatment with hydrocortisone or glucocorticoids reduce bone density?

1. Strand V, Simon LS. Low dose glucocorticoids in early rheumatoid arthritis. Clin Exp Rheumatol. 2003 Sep-Oct;21(5 Suppl 31):S186-90 (In this study it is “suggested that with appropriate monitoring and careful concomitant prophylactic therapy to prevent osteoporosis, adjunctive therapy using low dose glucocorticoids … may be a reasonable treatment plan for select patients”)

Studies with adverse effects of glucocorticoid treatment on bone density:


Studies where the use of glucocorticoids was associated with a reduction of bone density (Critics: the treatments were not counterbalanced by a supplement of anabolic hormones such as DHEA, androgen or female hormone or calcitonin therapy)

3. Saito JK, Davis JW, Wasnich RD, Ross PD. Users of low-dose glucocorticoids have increased bone loss rates: a longitudinal study, Calcif Tissue Int. 1995 Aug;57(2):115-9 (“The most common dose was equivalent to 5 mg/day of prednisone; fewer than 15% of users had taken doses equivalent to 10 mg/day or more”; Critics: the treatment was not counterbalanced by a supplement of anabolic hormones; patients were old : a mean of 64 yrs for women and 68 yrs for men, an age where the decline in anabolic hormones is important, leaving the body unprotected against any supplement of a catabolic hormone)


5. McKenzie R, Reynolds JC, O’Fallon A, Dale J, Deloria M, Blackwelder W, Straus SE. Decreased bone mineral density in low dose glucocorticoid administration in a randomized, placebo controlled trial. J Rheumatol. 2000 Sep;27(9):2222-6 (“a dose of 25 to 35 mg/day (equivalent to about 7.5 mg prednisone/day) for 12 weeks (causes) a mean decrease in bone mineral density from baseline of the lateral spine of -2.0% and a mean change of the anteroposterior spine of -0.8% compared to placebo +1.0% and +0.2%”; Critic: above 4 mg/day of prednisolone or 20 mg/day of hydrocortisone us, the bone density decreases unless a supplement of anabolic hormones is added)


7. Buckley LM, Leib ES, Cartularo KS, Vacek PM, Cooper SM. Effects of low dose corticosteroids on the bone mineral density of patients with rheumatoid arthritis. J Rheumatol. 1995 Jun;22(6):1055-9 (5-7 mg/day significantly reduces solely the bone density of the lumbar spine, not of the femoral neck, while 1-4 mg/day prednisone does not effect bone density of the lumbar spine, nor of the femoral neck)

8. Lipworth BJ. Systemic adverse effects of inhaled corticosteroid therapy: A systematic review and meta-analysis. Arch Intern Med 1999 May 10;159(9):941-55 (Inhaled corticosteroids in doses above 1.5 mg/d (0.75 mg/d for fluticasone propionate) may be associated with a significant reduction in bone density, although the risk for osteoporosis may be obviated by post-menopausal estrogen replacement therapy)

Studies with no effect of glucocorticoid treatment on bone density: studies with up to 58 months of treatment and 6 mg/day of methyprednisolone
9. Contreras LN, Rizzo L, Gomez RM, Zanchetta JR, Rossi MA, Kral M, Masini AM, Bruno OD. Long-term low-dose glucocorticoid therapy in hyperandrogenized women: utility and effects on bone mineral content and hypothalamic-pituitary-adrenocortical function. Horm Res. 1991;35(3-4):142-5 (*treatment with 1-6 mg oral evening doses of 16 beta methylprednisone for 12-58 months: absence of quantitative bone mass reduction and normal corticotrope reserve were observed even after 58 months of daily steroid administration*)


1-4 mg/day of prednisone does not effect the bone density of the lumbar spine or femoral neck, while 5-7 mg/day reduces significantly solely the bone density of the lumbar spine, not of the femoral neck


A risk of bone loss may be avoided with a substitution dosage of 20 mg or even 15 mg hydrocortisone per day


Studies with beneficial effect of glucocorticoid treatment on bones

Beneficial effect of prednisolone on bone density in rheumatoid arthritis


Beneficial effect of cortisol against bone resorption in vitro


16. Atkins D, Peacock M. A comparison of the effects of the calcitonins, steroid hormones and thyroid hormones on the response of bone to parathyroid hormone in tissue culture. J Endocrinol. 1975 Mar;64(3):573-83 (cortisol at high doses blocks the increase in bone resorption of parathyroid hormone)

It is important to join treatments with anabolic hormones that counterbalance any adverse effects of glucocorticoid treatment

Studies of bone-protective combinations of an anabolic hormone treatment with glucocorticoids

With calcitonin


With female hormone replacement


With GH


With vitamin D


With biphosphonates


With sodium fluoride


Exercise


35. (6 months of resistance exercise, consisting of low back exercise that isolates the lumbar spine and a regimen of variable resistance exercises, restores BMD toward pretransplantation levels.)

Only very few patients on glucocorticoids (average dose 10 mg/day) follow an adjuvant therapy for prevention of osteoporosis (vit. D, hormone replacement)

36. Hougardy DM, Peterson GM, Bleasal MD, Randall CT. Is enough attention being given to the adverse effects of corticosteroid therapy? J Clin Pharm Ther. 2000 Jun;25(3):227-34 (Only 21% of all patients on oral corticosteroids and 31% of those who had been taking oral corticosteroids for at least one year were
receiving medication for osteoporosis prevention, and only 15% of women over 45 years of age and on oral corticosteroid therapy were taking hormone replacement therapy.

37. Buckley LM, Marquez M, Feezor R, Ruffin DM, Benson LL. Prevention of corticosteroid-induced osteoporosis: results of a patient survey. Arthritis Rheum. 1999 Aug;42(8):1736-9 (“29 % reported having a bone density test. 29% were taking calcium supplements, and 45% were receiving vitamin D. 40 % of postmenopausal (PMP) women were receiving HRT and 14%, bisphosphonate treatment. 42 % of PMP women were receiving no preventive treatment.”)

3. Can glucocorticoids cause memory loss and facilitate the occurrence of Alzheimer’s disease?

Arguments against the use of glucocorticoids in case of memory loss

The worsening of the memory or neurons necessary for memory with cortisol or other glucocorticoid treatment


Data that glucocorticoid treatment has no effects, adverse or beneficial, in case of memory loss

No effect of glucocorticoids in Alzheimer’s disease


Arguments that glucocorticoid treatment may be beneficial in case of memory loss

Reduced glucocorticoid response in Alzheimer’s disease


Glucocorticoid treatment improves the memory for stressful events or avoidance reactions


Anecdotal report on dementia reversed with glucocorticoid treatment