The International Hormone Society

www.intlhormonesociety.org

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

41. Bouwer C, Claassen J, Dinans TG, Nemeroff CB. Prednisone augmentation in treatment-resistant depression with fatigue and hypocortisolaemia: a case series. Depress Anxiety. 2000;12(1):44-50
42. Cleare AJ, Miell J, Heap E, Sookdeo S, Young L, Malhi GS, O'Keane V. Hypothalamo-pituitary-adrenal axis dysfunction in chronic fatigue syndrome, and the effects of low-dose hydrocortisone therapy. J Clin Endocrinol Metab. 2001 Aug;86(8):3545-54
43. Cleare AJ, Blair D, Chambers S, Wessely S. Urinary free cortisol in chronic fatigue syndrome. Am J Psychiatry. 2001 Apr;158(4):641-3
44. van der Pompe G, Bernards N, Kavelaars A, Heijnen C. An exploratory study into the effect of exhausting bicycle exercise on endocrine and immune responses in post-menopausal women: relationships between vigour and plasma cortisol concentrations and lymphocyte proliferation following exercise. Int J Sports Med. 2001 Aug;22(6):447-53
45. Akerstedt T, Palmblad J, de la Torre B, Marana R, Gillberg M. Adrenocortical and gonadal steroids during sleep deprivation. Sleep. 1980;3(1):23-30
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
47. Bianchi GP, Grossi G, Bargossi AM. May peripheral and central fatigue be correlated? Can we monitor them by means of clinical laboratory tools? J Sports Med Phys Fitness. 1997 Sep;37(3):194-9
48. Pruessner JC, Hellhammer DH, Kirschbaum C. Burnout, perceived stress, and cortisol responses to awakening. Psychosom Med. 1999 Mar-Apr;61(2):197-204
49. Nicolson NA, van Diest R. Salivary cortisol patterns in vital exhaustion. J Psychosom Res. 2000 Nov;49(5):335-42
50. MacHale SM, Cavanagh JT, Bennie J, Carroll S, Goodwin GM, Lawrie SM. Diurnal variation of adrenocortical activity in chronic fatigue syndrome. Neuropsychobiology. 1998 Nov;38(4):213-7
51. Bower JE, Ganz PA, Aziz N, Fahey JL. Fatigue and proinflammatory cytokine activity in breast cancer survivors. Psychosom Med. 2002 Jul-Aug;64(4):604-11
52. Subramanian S, Goker H, Kanji A, Sweeney H. Clinical adrenal insufficiency in patients receiving megestrol therapy. Arch Intern Med. 1997 May 12;157(9):1008-11
53. Dore MX, de La Blanchardiere A, Lesprit P, David F, Beressi JP, Fiet J, Sicard D, Decazes JM. Peripheral adrenal insufficiency in AIDS. Rev Med Interne. 1998 Jan;19(1):23-8
54. Piedrola G, Casado JL, Lopez E, Moreno A, Perez-Elias MJ, Garcia-Robles R. Clinical features of adrenal insufficiency in patients with acquired immunodeficiency syndrome. Clin Endocrinol (Oxf). 1996 Jul;45(1):97-101
55. Albeaux-Fernet M, Bugard P, Romani JD. Excretion of urinary corticoids in conditions of chronic asthenia. J Clin Endocrinol Metab. 1957 Apr;17(4):519-33
56. Demitrack MA, Dale JK, Straus SE, Laue L, Listwak SJ, Kruesi MJ, Chrousos GP, Gold PW. Evidence for impaired activation of the hypothalamic-pituitary-adrenal axis in patients with chronic fatigue syndrome. J Clin Endocrinol Metab. 1991 Dec;73(6):1224-34
57. Cleare AJ, Bearn J, Allain T, McGregor A, Wessely S, Murray RM, O'Keane V. Contrasting neuroendocrine responses in depression and chronic fatigue syndrome. J Affect Disord. 1995 Aug 18;34(4):283-9
58. Strickland P, Morriss R, Wearden A, Deakin B. A comparison of salivary cortisol in chronic fatigue syndrome, community depression and healthy controls. J Affect Disord. 1998 Jan;47(1-3):191-4
59. Scott LV, Dinans TG. Urinary free cortisol excretion in chronic fatigue syndrome, major depression and in healthy volunteers. J Affect Disord. 1998 Jan;47(1-3):49-54

60. Bearn J, Allain T, Coskeran P, Munro N, Butler J, McGregor A, Wessely S. Neuroendocrine responses to d-fenfluramine and insulin-induced hypoglycemia in chronic fatigue syndrome. Biol Psychiatry. 1995 Feb 15;37(4):245-52
61. Scott LV, Medbak S, Dinans TG. The low dose ACTH test in chronic fatigue syndrome and in health. Clin Endocrinol (Oxf). 1998 Jun;48(6):733-7
62. Scott LV, Medbak S, Dinans TG. Desmopressin augments pituitary-adrenal responsivity to corticotropin-releasing hormone in subjects with chronic fatigue syndrome and in healthy volunteers. Biol Psychiatry. 1999 Jun 1;45(11):1447-54
63. Altemus M, Dale JK, Michelson D, Demitrack MA, Gold PW, Straus SE. Abnormalities in response to vasopressin infusion in chronic fatigue syndrome. Psychoneuroendocrinology. 2001 Feb;26(2):175-88
64. Gaab J, Huster D, Peisen R, Engert V, Schad T, Schurmeyer TH, Ehlert U. Low-dose dexamethasone suppression test in chronic fatigue syndrome and health. Psychosom Med. 2002 Mar-Apr;64(2):311-8
65. Parker AJ, Wessely S, Cleare AJ. The neuroendocrinology of chronic fatigue syndrome and fibromyalgia. Psychol Med. 2001 Nov;31(8):1331-45
66. Roberts AD, Wessely S, Chalder T, Papadopoulos A, Cleare AJ. Salivary cortisol response to awakening in chronic fatigue syndrome. Br J Psychiatry. 2004 Feb;184:136-41

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

67. Whitcomb JE, Findling JW, Raff H, Harnsher K. Randomized trial of oral hydrocortisone and its effect on emergency physicians during night duty. WMJ. 2000 Oct;99(7):37-41
68. Bruera E, Roca E, Cedaro L, Carraro S, Chacon R. Action of oral methylprednisolone in terminal cancer patients: a prospective randomized double-blind study. Cancer Treat Rep. 1985 Jul-Aug;69(7-8):751-4
69. Riedel M, Wiese A, Schurmeyer TH, Brabant G. Quality of life in patients with Addison's disease: effects of different cortisol replacement modes. Exp Clin Endocrinol. 1993;101(2):106-11
70. Rubin GJ, Hotopf M. Systematic review and meta-analysis of interventions for postoperative fatigue. Br J Surg. 2002 Aug;89(8):971-84

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

71. Scott LV, Dinan TG. Urinary free cortisol excretion in chronic fatigue syndrome, major depression and in healthy volunteers. J Affect Disord; 1998 Jan;47(1-3):49-54
72. Yerevanian BI, Woolf PD, Iker HP. Plasma ACTH levels in depression before and after recovery: relationship to the dexamethasone suppression test. Psychiatry Res. 1983 Nov;10(3):175-81
73. Yehuda R, Boisoneau D, Mason JW, Giller EL. Glucocorticoid receptor number and cortisol excretion in mood, anxiety, and psychotic disorders. Biol Psychiatry. 1993 Jul 1-15;34(1-2):18-25

Depression: the improvement with cortisol or other glucocorticoid treatments

74. Goodwin GM, Muir WJ, Seckl JR, Bennie J, Carroll S, Dick H, Fink G. The effects of cortisol infusion upon hormone secretion from the anterior pituitary and subjective mood in depressive illness and in controls. J Affect Disord. 1992 Oct;26(2):73-83
75. O'Dwyer AM, Lightman SL, Marks MN, Checkley SA. Treatment of major depression with metyrapone and hydrocortisone. J Affect Disord. 1995 Feb 21;33(2):123-8
76. Adunsky A, Berkowitz M, Waller A. Corticosteroids in terminal cancer. Harefuah. 1995 Mar 1;128(5):278-80, 335

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

77. Giese-Davis J, Sephton SE, Abercrombie HC, Duran RE, Spiegel D. Repression and high anxiety are associated with aberrant diurnal cortisol rhythms in women with metastatic breast cancer. Health Psychol. 2004 Nov;23(6):645-50
78. Rondo PH, Vaz AJ, Moraes F, Tomkins A. The relationship between salivary cortisol concentrations and anxiety in adolescent and non-adolescent pregnant women. Braz J Med Biol Res. 2004 Sep;37(9):1403-9
79. Feder A, Coplan JD, Goetz RR, Mathew SJ, Pine DS, Dahl RE, Ryan ND, Greenwald S, Weissman MM. Twenty-four-hour cortisol secretion patterns in prepubertal children with anxiety or depressive disorders. Biol Psychiatry. 2004 Aug 1;56(3):198-204
80. Dorn LD, Susman EJ, Petersen AC. Cortisol reactivity and anxiety and depression in pregnant adolescents: a longitudinal perspective. Psychoneuroendocrinology. 1993;18(3):219-39

Anxiety: the improvement with cortisol or other glucocorticoid treatment

81. Schelling G, Roozendaal B, De Quervain DJ. Can posttraumatic stress disorder be prevented with glucocorticoids? Ann NY Acad Sci. 2004 Dec;1032:158-66

82. Schelling G, Kilger E, Roozendaal B, de Quervain DJ, Briegel J, Dagge A, Rothenhausler HB, Krauseneck T, Nollert G, Kapfhammer HP. Stress doses of hydrocortisone, traumatic memories, and symptoms of posttraumatic stress disorder in patients after cardiac surgery: a randomized study. Biol Psychiatry. 2004 Mar 15;55(6):627-33

Memory improvement for stressful events or avoidance reactions with glucocorticoid treatment

83. Peeters BW, Broekkamp CL. Involvement of corticosteroids in the processing of stressful life-events. A possible implication for the development of depression. J Steroid Biochem Mol Biol. 1994 Jun;49(4-6):417-27
84. Sandi C, Rose SP, Mileusnic R, Lancashire C. Corticosterone facilitates long-term memory formation via enhanced glycoprotein synthesis. Neuroscience. 1995 Dec;69(4):1087-93
85. Roozendaal B, Carmi O, McGaugh JL. Adrenocortical suppression blocks the memory-enhancing effects of amphetamine and epinephrine. Proc Natl Acad Sci U S A. 1996 Feb 20;93(4):1429-33.
86. Roozendaal B, McGaugh JL. The memory-modulatory effects of glucocorticoids depend on an intact stria terminalis. Brain Res. 1996 Feb 19;709(2):243-50
87. Roozendaal B, McGaugh JL. Amygdaloid nuclei lesions differentially affect glucocorticoid-induced memory enhancement in an inhibitory avoidance task. Neurobiol Learn Mem. 1996 Jan;65(1):1-8

Anecdotal report on dementia reversed with glucocorticoid treatment

88. Basavaraju N, Phillips SL. Cortisol deficient state. A cause of reversible cognitive impairment and delirium in the elderly.J Am Geriatr Soc. 1989 Jan;37(1):49-51

Sleep disorder: the association with cortisol levels

89. Spath-Schwalbe E, Scholler T, Kern W, Fehm HL, Born J. Nocturnal adrenocorticotropin and cortisol secretion depends on sleep duration and decreases in association with spontaneous awakening in the morning. J Clin Endocrinol Metab. 1992 Dec;75(6):1431-5

2. <u>Cortisol is important for optimal body appearance</u>

Hirsutism: the improvement with glucocorticoid treatment

90. Carmina E, Lobo RA. Peripheral androgen blockade versus glandular androgen suppression in the treatment of hirsutism. Obstet Gynecol. 1991 Nov;78(5 Pt 1):845-9
91. Cunningham SK, Loughlin T, Culliton M, McKenna TJ. Plasma sex hormone-binding globulin and androgen levels in the management of hirsute patients. Acta Endocrinol (Copenh). 1983 Nov;104(3):365-71
92. Abraham GE, Maroulis GB, Boyers SP, Buster JE, Magyar DM, Elsner CW. Dexamethasone suppression test in the management of hyperandrogenized patients. Obstet Gynecol. 1981 Feb;57(2):158-65
93. Wieland RG, Zorn E. Effect of chronic combined glucocorticoid and estrogen on serum androgens and androgen binding in hirsutism. Cutis. 1979 Apr;23(4):458-60
94. Casey JH. Chronic treatment regimens for hirsutism in women: effect on blood production rates of testosterone and on hair growth. Clin Endocrinol (Oxf). 1975 May;4(3):313-25

Skin disorders: the improvement with glucocorticoid treatment

95. Pollack CV Jr, Romano TJ. Outpatient management of acute urticaria: the role of prednisone. Ann Emerg Med. 1995 Nov;26(5):547-51

3. <u>Cortisol may oppose age-related diseases</u>

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)*

Hyperhomocystlnemia: the improvement with glucocorticoid treatment

97. Lazzerini PE, Capecchi PL, Bisogno S, Galeazzi M, Marcolongo R, Pasini FL.Reduction in plasma homocysteine level in patients with rheumatoid arthritis given pulsed glucocorticoid treatment. Ann Rheum Dis. 2003 Jul;62(7):694-5
98. Kim MH, Kim E, Passen EL, Meyer J, Kang SS. Cortisol and estradiol: nongenetic factors for hyperhomocyst(e)inemia. Metabolism. 1997 Mar;46(3):247-9

Heart disease: the improvement with glucocorticoid treatment

99. Morrison J, Maley T, Reduto L, Victa C, Pyros I, Brandon J, Gulotta S. Effect of methylprednisolone on predicted myocardial infarction size in man. Crit Care Med. 1975 May-Jun;3(3):94-102

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

100. Hallgren R, Berne C. Glucose intolerance in patients with chronic inflammatory diseases is normalized by glucocorticoids. Acta Med Scand. 1983;213(5):351-5
101. Tanaka S, Kobayashi T, Nakanishi K, Okubo M, Murase T, Hashimoto M, Takeuchi K. Corticosteroid-responsive diabetes mellitus associated with autoimmune pancreatitis. Lancet. 2000 Sep 9;356(9233):910-1

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

102. Ozdemir H, Karacorlu M, Karacorlu SA. Regression of serous macular detachment after intravitreal triamcinolone acetonide in patients with diabetic macular edema. Am J Ophthalmol. 2005 Aug;140(2):251-5
103. Er H, Yilmaz H. Intravitreal cortisone injection for refractory diffuse diabetic macular edema. Ophthalmologica. 2005 Nov-Dec;219(6):394-400
104. Martidis A, Duker JS, Greenberg PB, Rogers AH, Puliafito CA, Reichel E, Baumal C. Intravitreal triamcinolone for refractory diabetic macular edema. Ophthalmology. 2002 May;109(5):920-7
105. Jonas JB, Kreissig I, Sofker A, Degenring RF. Intravitreal injection of triamcinolone for diffuse diabetic macular edema. Arch Ophthalmol. 2003 Jan;121(1):57-61
106. Jonas JB, Kreissig I, Sofker A, Degenring RF. Intravitreal injection of triamcinolone for diffuse diabetic macular edema. Arch Ophthalmol. 2003 Jan;121(1):57-61
107. Al-Haddad CE, Jurdi FA, Bashshur ZF. Intravitreal triamcinolone acetonide for the management of diabetic papillopathy. Am J Ophthalmol. 2004 Jun;137(6):1151-3
108. Ciardella AP, Klancnik J, Schiff W, Barile G, Langton K, Chang S. Intravitreal triamcinolone for the treatment of refractory diabetic macular oedema with hard exudates: an optical coherence tomography study. Br J Ophthalmol. 2004 Sep;88(9):1131-6
109. Ozkiris A, Evereklioglu C, Erkilic K, Tamcelik N, Mirza E. Intravitreal triamcinolone acetonide injection as primary treatment for diabetic macular edema. Eur J Ophthalmol. 2004 Nov-Dec;14(6):543-9

Rheumatism: the association with lower serum cortisol levels

110. Hedman M, Nilsson E, de la Torre B. Low blood and synovial fluid levels of sulpho-conjugated steroids in rheumatoid arthritis. Clin Exp Rheumatol. 1992 Jan-Feb;10(1):25-30

Rheumatism: the improvement with cortisol or other glucocorticoid treatments

111. Criswell LA, Saag KG, Sems KM, Welch V, Shea B, Wells G, Suarez-Almazor ME. Moderate-term, low-dose corticosteroids for rheumatoid arthritis. Cochrane Database Syst Rev. 2000;(2):CD001158
112. Stenberg VI, Fiechtner JJ, Rice JR, Miller DR, Johnson LK. Endocrine control of inflammation: rheumatoid arthritis double-blind, crossover clinical trial. Int J Clin Pharmacol Res. 1992;12(1):11-8
113. Kirwan JR, Lim KK. Low dose corticosteroids in early rheumatoid arthritis. Can these drugs slow disease progression? Drugs Aging. 1996 Mar;8(3):157-61
114. Gerlag DM, Haringman JJ, Smeets TJ, Zwinderman AH, Kraan MC, Laud PJ, Morgan S, Nash AF, Tak PP. Effects of oral prednisolone on biomarkers in synovial tissue and clinical improvement in rheumatoid arthritis. Arthritis Rheum. 2004 Dec;50(12):3783-91
115. Koski JM, Hermunen H. Intra-articular glucocorticoid treatment of the rheumatoid wrist. An ultrasonographic study. Scand J Rheumatol. 2001;30(5):268-70
116. Ehrlich HP, Tarver H, Hunt TK. Effects of vitamin A and glucocorticoids upon inflammation and collagen synthesis. Ann Surg. 1973 Feb;177(2):222-7
117. Da Silva JA, Bijlsma JW. Optimizing glucocorticoid therapy in rheumatoid arthritis. Rheum Dis Clin North Am. 2000 Nov;26(4):859-80
118. Kirwan JR. The effect of glucocorticoids on joint destruction in rheumatoid arthritis. The Arthritis and Rheumatism Council Low-Dose Glucocorticoid Study Group. N Engl J Med. 1995 Jul 20;333(3):142-6
119. Hickling P, Jacoby RK, Kirwan JR. Joint destruction after glucocorticoids are withdrawn in early rheumatoid arthritis. Arthritis and Rheumatism Council Low Dose Glucocorticoid Study Group. Br J Rheumatol. 1998 Sep;37(9):930-6

Bone density in rheumatoid disease: Reduced loss with glucocorticoid treatment

120. Haugeberg G, Strand A; Kvien TK, Kirwan JR. 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

Neurodegenerative diseases: the improvement with glucocorticoid treatment

121. Hommes OR, Barkhof F, Jongen PJ, Frequin ST. Methylprednisolone treatment in multiple sclerosis: effect of treatment, pharmacokinetics, future. Mult Scler. 1996 Jul;1(6):327-8

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

123. Leonovich AL, Gitkina LS. Use of glucocorticoid hormones in multiple sclerosis. Zh Nevropatol Psikhiatr Im S S Korsakova. 1976 Sep;76(9):1318-22

Cancer: the improvement with glucocorticoids

124. Gaynon PS, Lustig RH. The use of glucocorticoids in acute lymphoblastic leukemia of childhood Molecular, cellular, and clinical considerations. J Pediatr Hematol Oncol. 1995 Feb;17(1):1-12

125. Walsh D, Avashia J. Glucocorticoids in clinical oncology. Cleve Clin J Med. 1992 Sep-Oct;59(5):505-15.

126. Nishimura K, Nonomura N, Yasunaga Y, Takaha N, Inoue H, Sugao H, Yamaguchi S, Ukimura O, Miki T, Okuyama A.Low doses of oral dexamethasone for hormone-refractory prostate carcinoma. Cancer. 2000 Dec 15;89(12):2570-6

Cancer: palliative help from glucocorticoid treatment

127. Kobayashi T, Jo Y, Ikegami M, Furukawa Y, Morioka M, Tanaka H, Kinugawa K, Ohta S. Clinical evaluation of low dose glucocorticoid therapy for hormone-refractory prostate cancer. Nippon Hinyokika Gakkai Zasshi. 2000 Apr;91(4):479-84

128. Bruera E, Roca E, Cedaro L, Carraro S, Chacon R. Action of oral methylprednisolone in terminal cancer patients: a prospective randomized double-blind study. Cancer Treat Rep. 1985 Jul-Aug;69(7-8):751-4

4. <u>Cortisol is necessary for life</u>:

Lifespan: the association with cortisol levels

129. Soni A, Pepper GM, Wyrwinski PM, Ramirez NE, Simon R, Pina T, Gruenspan H, Vaca CE. Adrenal insufficiency occurring during septic shock: incidence, outcome, and relationship to peripheral cytokine levels. Am J Med. 1995 Mar;98(3):266-71

130. Moran JL, Chapman MJ, O'Fathartaigh MS, Peisach AR, Pannall PR, Leppard P. Hypocortisolaemia and adrenocortical responsiveness at onset of septic shock. Intensive Care Med. 1994 Aug;20(7):489-95

Lifespan: the improvement with cortisol or other glucocorticoid treatments

131. Imperiale TF, McCullough AJ. Do corticosteroids reduce mortality from alcoholic hepatitis? A meta-analysis of the randomized trials. Ann Intern Med. 1990 Aug 15;113(4):299-307

132. Gagnon S, Boota AM, Fischl MA, Baier H, Kirksey OW, La Voie L. Corticosteroids as adjunctive therapy for severe Pneumocystis carinii pneumonia in the acquired immunodeficiency syndrome. A double-blind, placebo-controlled trial. N Engl J Med. 1990 Nov 22;323(21):1444-50

<u>II) TOOLS FOR DIAGNOSIS OF CORTISOL DEFICIENCY</u>

1) Clinical cortisol evaluation

133. Sokol AF. Evaluation of clinical symptoms of Addison's disease. Probl Endokrinol (Mosk). 1985 Jul-Aug;31(4):20-2

134. Studer H, Straub W. Steroid withdrawal syndrome. A current problem of outpatient medicine. Schweiz Med Wochenschr. 1981 Oct 3;111(40):1462-7

135. Yehuda R, Golier JA, Kaufman S. Circadian rhythm of salivary cortisol in Holocaust survivors with and without PTSD. Am J Psychiatry. 2005 May;162(5):998-1000

136. Neylan TC, Brunet A, Pole N, Best SR, Metzler TJ, Yehuda R, Marmar CR. PTSD symptoms predict waking salivary cortisol levels in police officers. Psychoneuroendocrinology. 2005 May;30(4):373-81.

137. Ehlert U, Nater UM, Bohmelt A. High and low unstimulated salivary cortisol levels correspond to different symptoms of functional gastrointestinal disorders. J Psychosom Res. 2005 Jul;59(1):7-10

138. Shirtcliff EA, Granger DA, Booth A, Johnson D. Low salivary cortisol levels and externalizing behavior problems in youth. Dev Psychopathol. 2005 Winter;17(1):167-84

139. Werbel SS, Ober KP. Acute adrenal insufficiency. Endocrinol Metab Clin North Am. 1993 Jun;22(2):303-28

2) Serum cortisol tests

Serum cortisol

140. Lambert WE, De Slypere JP, Jonckheere JA, Vermeulen A, De Leenheer AP. Improved liquid chromatographic determination of serum cortisol with double internal standardization compared to radioimmunoassay and fluorometry, and evaluated by isotope dilution/mass spectrometry. Anal Biochem. 1983 Oct 1;134(1):216-23
141. Stalla GK, Giesemann G, Muller OA, Wood WG, Scriba PC. The development of a direct homologous radioimmunoassay for serum cortisol. J Clin Chem Clin Biochem. 1981 Jul;19(7):427-34
142. Valdes R Jr, Wills MR, Savory J. Evaluation of an automated radioimmunoassay for serum cortisol. Ann Clin Lab Sci. 1980 Nov-Dec;10(6):508-14
143. Canalis E, Caldarella AM, Reardon GE. Serum cortisol and 11 deoxycortisol by liquid chromatography: clinical studies and comparison with radioimmunoassay. Clin Chem. 1979 Oct;25(10):1700-3

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

144. Fernandez-Real JM, Pugeat M, Lopez-Bermejo A, Bornet H, Ricart W. Corticosteroid-binding globulin affects the relationship between circulating adiponectin and cortisol in men and women. Metabolism. 2005 May;54(5):584-9.
145. Glyda A, Kozak W, Wasko R, Junik R, Krawczyk J.Radioimmunologic methods for determining cortisol binding globulin-CBG in human serum. Ginekol Pol. 1996 Nov;67(11):545-7
146. Wiegratz I, Jung-Hoffmann C, Kuhl H. Effect of two oral contraceptives containing ethinylestradiol and gestodene or norgestimate upon androgen parameters and serum binding proteins. Contraception. 1995 Jun;51(6):341-6
147. Hammerstein J, Daume E, Simon A, Winkler UH, Schindler AE, Back DJ, Ward S, Neiss A. Influence of gestodene and desogestrel as components of low-dose oral contraceptives on the pharmacokinetics of ethinyl estradiol (EE2), on serum CBG and on urinary cortisol and 6 beta-hydroxycortisol. Contraception. 1993 Mar;47(3):263-81

Serum ACTH- and CRF-stimulation tests

148. Kelestimur F, Akgun A, Gunay O. A comparison between short synacthen test and depot synacthen test in the evaluation of cortisol reserve of adrenal gland in normal subjects. J Endocrinol Invest. 1995 Dec;18(11):823-6.

3) Salivary cortisol

149. Gozansky WS, Lynn JS, Laudenslager ML, Kohrt WM. Salivary cortisol determined by enzyme immunoassay is preferable to serum total cortisol for assessment of dynamic hypothalamic--pituitary-adrenal axis activity. Clin Endocrinol (Oxf). 2005 Sep;63(3):336-41
150. Garde AH, Hansen AM. Long-term stability of salivary cortisol. Scand J Clin Lab Invest. 2005;65(5):433-6
151. Patel RS, Shaw SR, Macintyre H, McGarry GW, Wallace AM. Production of gender-specific morning salivary cortisol reference intervals using internationally accepted procedures. Clin Chem Lab Med. 2004;42(12):1424-9
152. Patel RS, Shaw SR, McIntyre HE, McGarry GW, Wallace AM. Morning salivary cortisol versus short Synacthen test as a test of adrenal suppression. Ann Clin Biochem. 2004 Sep;41(Pt 5):408-10

4) 24-hour urine cortisol tests

Urinary cortisol and 17-OH-steroids

153. Bailey E, West HF. The secretion, interconversion and catabolism of cortisol, cortisone and some of the metabolites in man. Acta endocrinol. 1969;62:339-59
154. Flood C, Layne DS, Ramcharan S, Rossipal E, Tait JF, Tait SA. An investigation of the urinary metabolites and secretion rates of aldosterone and cortisol in man and a description of methods for their measurement. Acta Endocrinol (Copenh). 1961 Feb;36:237-64
155. Romanoff LP, Joyce MA, Rodriguez RM, Seelye JM, Parent C, Pincus G. The urinary excretion of tetrahydrocortisol, 3-alpha-allotetrahydrocortisol and tetrahydrocortisone in young and elderly men and women. J Clin Endocrinol Metab. 1958;18:1285-95
156. Meikle AW, Takiguchi H, Mizutani S, Tyler FH, West CD. Urinary cortisol excretion determined by competitive protein-binding radioassay: a test of adrenal cortical function. J Lab Clin Med. 1969 Nov;74(5):803-12
157. Murphy BE. Clinical evaluation of urinary cortisol determinations by competitive protein-binding radioassay. J Clin Endocrinol Metab. 1968 Mar;28(3):343-8
158. Murphy D, West HF. Routine multipurpose gas chromatographic assay for urinary corticosteroids. J Clin Pathol. 1968 May;21(3):372-5

159. Dyrenfurth I, Sybulski S, Notchev V, Beck JC, Venning EH. Urinary corticosteroid excretion patterns in patients with adrenocortical dysfunction. J Clin Endocrinol. Metab.1958;18:391-3
160. Romanoff LP, Rodriguez RM, Joyce MA, Seelye JM, Pincus G. Determination of tetrahydrocortisol and tetrahydrocortisone in the urine of normal and schizophrenic men. J Clin Endocrinol Met. 1956;17:777-85
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
162. Jaselius RE, Kenny FM. Urinary free cortisol excretion during growth and aging: Correlation with cortisol production rate and 17-hydroxycorticosteroid excretion. Metabolism. 1974;23:847-52
163. Crapo L. Cushing's syndrome: A review of diagnostic tests. Metabolism.1979; 28: 955-77
164. Gilliland PF, Ibarra JD Jr, Thompson JQ, MacMurry JF Jr. Cushing's syndrome: a prospective study of diagnostic methods. Am J Med. 1973 Nov;55(5):621-30
165. Burke CW. Hormones in urine: Uses and misuses. J R Coll Phvsicians Lond. 1974:8:335-54
166. Persky H, Zuckennan M, Curtis GC. Endocrine function in emotionally disturbed and normal men. J Nerv Ment Dis. 1968; 146:488-97
167. Burke CW, Beardwell CG: Cushing's syndrome. An evaluation of the clinical usefulness ofurinary free cortisol and other urinary steroid measurements in diagnosis. Q J Med. 1973; 42:175-204
168. Streeten DHP, Stevenson CT, Dalakos TG, et al. The diagnosis of hypercortisolism: biochemical criteria differentiating patients from lean and obese Donnai subjects and from females on oral contraceptives. J Clin Endocrinol Metab. 1969; 29:1191-211
169. Franks RC. Diurnal variation of plasma 17 -hydroxcorticosteroids in children. J Clin Endocrinol Metab. 1967;27:75-78
170. Silverberg A, Rizzo F, Krieger DT. Nyctohemeral periodicity of plasma 17 -OHCS levels in elderly subjects. J Clin Endocrinol Metab. 1968;28:1661-3
171. Migeon CI, Tyler FA, Mahone JP, Bliss EL, Samuels LT. The diurnal variation of plasma levels and urinary excretion of 17-hydroxycorticosteroids in normal subjects, night workers and blind subjects. J Clin Endocrinol. 1956;622-33
172. Hetzel BSD., Scbottstaedt WW, Wolff HG. Changes in urinary 17-bydroxycorticosteroid excretion during stressful life experiences in man. J Clin Endocrinol. 1954;57-68
173. Sandberg AA, Chang E, Slaunwhite WR. The conversion of 4-C^{14}-cortisol to C^{l4}-l7-ketosteroids. J Clin Endocrinol Metab. 1957;17:437-40
174. Nakamura 1, Yakata M. Age- and sex-related differences in urinary cortisol levels. Clin Chim Acta. 1984;137:77-80
175. Invitti C, Pecori Giraldi F, Dubini A, De Martin M, Cavagnini F. Increased urinary free cortisol and decreased serum corticosteroid-binding globulin in polycystic ovary syndrome. Acta Endocrinol (Copenh). 1991 Jul;125(1):28-32
176. Garces L Y, Kenny FM, Drash A, Taylor FA. Cortisol secretion rate during fasting of obese adolescent subjects. J Clin Endocrinol Metab. 1968; 28:1843-7
177. Adrenocortical hormones. Scientific Tables (Documenta Geigy). 6th ed. Diem K (ed.). Basle. Switserland
178. Huseby RA, Reed FC, Smith TE. Effects of semistarvation and water deprivation on adrenal cortical function and corticosteroid metabolism. J Appl Physiol. 1959;14:31-6
179. Smith SR, Bledsoe T, Chihetri MK. Cortisol metabolism and the pituitary-adrenal axis in adults with protein-calorie malnutrition. J Clin Endocrinol Metab. 1975;40:43-52
180. Romanoff LP, Morris CW, Welch P, Rodriguez RM, Pincus G. The metabolism of cortisol and daily excretion of tetrahydrocortisol, allotetrahydrocortisol, tetrahydrocortisone and cortolone (20 alpha and 20 beta). J Clin Endocrinol Metab. 1961 Nov;21:1413-25
181. Brown H, Englert E, Wallach S. Metabolism of free and conjugated 17-hydroxycorticosteroids in subjects with thyroid disease. J Clin Endocrinol Metab. 1958;18:167-79
182. Hellman L, Bradlow HL, Zumoff B, Callagher TF. The influence of thyroid hormone on hydrocortisone production and metabolism. J Clin Endocrinol Metab. 1961 Oct;21:1231-47
183. Peterson RE, Nokes G, Chen PS, Black HL: Estrogens and adrenocortical function in man. J Clin Endocrinol Metab. 1960; 20:495-514
184. Maengwyn-Davies GD, Weiner R. Excretion of 17-hydroxycorticosteroids during the menstrual cycle. J Clin Endocrinol.1955; 1150-1
185. Grant SD, Pavlatos F, Forsham PH. Effects of estrogen therapy on cortisol metabolism. J Clin Endocrinol Metab. 1965;25:1057-66
186. Peterson RE. Adrenocortical steroid metabolism and adrenal cortical function in liver disease. J Clin Invest. 1960;39:320-31
187. McCann VJ, Fulton TT. Cortisol metabolism in chronic liver disease. J Clin Endocrinol Metab. 1975; 40:1038-44

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
189. Gallagher TF, Hellman L, Finkelstein J, Yoshida K, Weitzman ED, Roffwarg HD, Fukushima DK. Hyperthyroidism and cortisol secretion in man. J Clin Endocrinol Metab. 1972 Jun;34(6):919-27
190. Janches M, Dendukes D, Secal L, de la Balze FA. Effects of a bacterial pyrogen on the elimination of urinary 17-hydroxycorticosteroids in normal subjects. J Clin Endocrinol Metab. 1965; 17-9
191. Zumoff B, Bradlow HL, Fukushima DK, Hellman L. Increase in the tetrahydrocortisol-tetrahydrocortisone ratio from cortisol-4-14C: a nonspecific consequence of illness. J Clin Endocrinol Metab. 1974 Dec;39(6):1120-4
192. Hume DM, Nelson DH, Miller DW. Blood and urinary 17 -hydroxycorticosteroids in patients with severe burns. Ann Surg. 1956; 143 :316-29
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
194. Gardner LI. Urinary dehydroepiandrosterone in idiopathic hirsutism: influence of cortisone therapy. J Clin Endocrinol Met. 1953;18:1054-8
195. Wilkins L, Lewis RA, Klein R, and Rosemberg E. Die Wirkung von Cortison auf die Auscheidung der 17-ketosteroide und andere Steroide bei Patienten mit kongenitaler Nebennierenhyperplasie. [Effect of cortisone on excretion of 17-ketosteroids and other steroids in patients with congenital adrenal hyperplasia.] Helv Paediatr Acta. 1950 Nov;5(5):418-25
196. Gardner LI. Urinary dehydroepiandrosterone in idiopathic hirsutism: Influence of cortisone
197. therapy. J Clin Endocrinol Metab. 1953 Sep;13(9):1054-63. No abstract available.
198. Gardner LI, Migeon CJ. Urinary dehydroisoandrosterone in hyperadrenocorticism: influence of cortisone, hydrocortisone and ACTH. J Clin Endocrinol Metab. 1952 May;12(9):1117-39
199. Winterer J, Chrousos GP, Loriaux DL, Cutler GB Jr. Effect of hydrocortisone dose schedule on adrenal steroid secretion in congenital adrenal hyperplasia. J Pediatr. 1985 Jan;106(1):137-42
200. Burch WM. Urine free-cortisol determination: a useful tool in the management of chronic hypoadrenal states. JAMA. 1982;247:2002-4
201. Voccia E, Saenger P, Peterson RE, Rauh W, Gottesdiener K, Levine LS, New MI. 6 beta-Hydroxycortisol excretion in hypercortisolemic states. J Clin Endocrinol Metab. 1979 Mar;48(3):467-71
202. Rose LI, Williams GH, Jagger PI, Lauler DP. The 48-hour adrenocorticotrophin infusion test for adrenocortical insufficiency. Ann Intern Med. 1970 Jul;73(1):49-54
203. Ronzoni E. The excretion of dehydroepiandrosterone during adrenal stimulation with adrenocorticotropic hormone. J Clin Endocrinol Metab. 1952;12:527-41
204. Abu Haydar N, ST. Marc JR, Reddy WJ, Laidlaw JC, Thorn GW. Adrenocortical insufficiency with normal basallevels of urinary 17-hydroxycorticoids: diagnostic implications. J Clin Endocrinol Metab. 1958;121-33
205. Englert E, Brown H, Willardson DG, et al. Metabolism of free and conjugated 17-hydroxycorticosteroids in subjects with uremia. J Clin Endocrinol Metab. 1958 18:36-48
206. Pekkarinen A, Kasanen A. Plasma level, urinary excretion, and clearance of 17-0HCS in renal patients after intravenous cortisol injection. Acta Endocrinol. 1961;38:13-21

III) GLUCOCORTICOID TREATMENT

1) Glucocorticoid medications

Oral Hydrocortisone

207. Mah PM, Jenkins RC, Rostami-Hodjegan A, Newell-Price J, Doane A, Ibbotson V, Tucker GT, Ross RJ. Weight-related dosing, timing and monitoring hydrocortisone replacement therapy in patients with adrenal insufficiency. Clin Endocrinol (Oxf). 2004 Sep;61(3):367-75
208. van der Heide-Jalving M, Kamphuis PJ, van der Laan MJ, Bakker JM, Wiegant VM, Heijnen CJ, Veen S, van Bel F. Short- and long-term effects of neonatal glucocorticoid therapy: is hydrocortisone an alternative to dexamethasone? Acta Paediatr. 2003 Jul;92(7):827-35

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

209. Frey BM, Frey FJ. Clinical pharmacokinetics of prednisone and prednisolone. Clin Pharmacokinet. 1990 Aug;19(2):126-46
210. Czock D, Keller F, Rasche FM, Haussler U. Pharmacokinetics and pharmacodynamics of systemically administered glucocorticoids. Clin Pharmacokinet. 2005;44(1):61-98

Inhaled glucocorticoids

211. Kelly HW. Comparative potency and clinical efficacy of inhaled corticosteroids. Respir Care Clin N Am. 1999 Dec;5(4):537-53

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

214. Minneci PC, Deans KJ, Banks SM, Eichacker PQ, Natanson C. Meta-analysis: the effect of steroids on survival and shock during sepsis depends on the dose. Ann Intern Med. 2004 Jul 6;141(1):47-56.
215. Bliesener N, Steckelbroeck S, Redel L, Klingmuller D. Dose distribution in hydrocortisone replacement therapy has a significant influence on urine free cortisol excretion. Exp Clin Endocrinol Diabetes. 2003 Oct;111(7):443-6
216. Rohleder N, Wolf JM, Kirschbaum C. Glucocorticoid sensitivity in humans-interindividual differences and acute stress effects. Stress. 2003 Sep;6(3):207-22

217. Czock D, Keller F, Rasche FM, Haussler U. Pharmacokinetics and pharmacodynamics of systemically administered glucocorticoids. Clin Pharmacokinet. 2005;44(1):61-98 *("the clinical efficacy of low-dose glucocorticoid regimens might be increased with twice-daily glucocorticoid administration")*

218. Frey BM, Frey FJ. Clinical pharmacokinetics of prednisone and prednisolone. Clin Pharmacokinet. 1990 Aug;19(2):126-46 *("an alternate-day regimen with prednisone yields fewer biological effects")*

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 gluccorticoids 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")*
221. Minneci PC, Deans KJ, Banks SM, Eichacker PQ, Natanson C. Meta-analysis: the effect of steroids on survival and shock during sepsis depends on the dose. Ann Intern Med. 2004 Jul 6;141(1):47-56. *("The efficacy of steroids on septic shock: depends on the lower dose: benefit at low doses and increasing harm at higher doses and longer courses")*

3. Frequency of glucocorticoid treatment use

222. Gallant C, Kenny P. Oral glucocorticoids and their complications. A review. J Am Acad Dermatol. 1986 Feb;14(2 Pt 1):161-77 *(prescribed to over 7% of hospitalized patients. Of this group, some 17% may experience adverse effects)*

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

223. Ferrari E, Cravello L, Muzzoni B, Casarotti D, Paltro M, Solerte SB, Fioravanti M, Cuzzoni G, Pontiggia B, Magri F. Age-related changes of the hypothalamic-pituitary-adrenal axis: pathophysiological correlates. Eur J Endocrinol. 2001 Apr;144(4):319-29

5. Glucocorticoid treatment: interferences

224. Frey BM, Frey FJ. Clinical pharmacokinetics of prednisone and prednisolone. Clin Pharmacokinet. 1990 Aug;19(2):126-46
225. Gambertoglio JG, Amend WJ Jr, Benet LZ. Pharmacokinetics and bioavailability of prednisone and prednisolone in healthy volunteers and patients: a review. J Pharmacokinet Biopharm. 1980 Feb;8(1):1-52
226. Abernethy DR, Greenblatt DJ. Drug disposition in obese humans. An update. Clin Pharmacokinet. 1986 May-Jun;11(3):199-213 *(the volume of distribution is in obese persons moderately increased for prednisolone)*

227. Gerl H, Rohde W, Biering H, Schulz N, Lochs H. Food-dependent Cushing syndrome of long standing with mild clinical features Dtsch Med Wochenschr. 2000 Dec 22;125(51-52):1565-8.

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, Buttgereit 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)")*

230. McConnell EM, Bell PM, Hadden DR, McCance DR, Sheridan B, Atkinson AB. Prevalence of diabetes and impaired glucose tolerance in adult hypopituitarism on low dose oral hydrocortisone replacement therapy. Clin Endocrinol (Oxf). 2001 May;54(5):593-9

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

232. Bey-Omar F, Feit JP, Forest MG, David M. Aggravation of salt loss due to hydrocortisone in the first days of treatment of congenital adrenal hyperplasia caused by 21-hydroxylase deficiency. Pediatrie. 1983 Mar;38(2):77-86

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

233. Ventura MT, Muratore L, Calogiuri GF, Dagnello M, Buquicchio R, Nicoletti A, Altamura M, Sabba C, Tursi A. Allergic and pseudoallergic reactions induced by glucocorticoids: a review. Curr Pharm Des. 2003;9(24):1956-64

Adverse effects of higher doses of glucocorticoids

234. Gallant C, Kenny P. Oral glucocorticoids and their complications. A review. J Am Acad Dermatol. 1986 Feb;14(2 Pt 1):161-77 *(prescribed to over 7% of hospitalized patients. Of this group, some 17% may experience adverse effects)*

235. del Rincon I, O'Leary DH, Haas RW, Escalante A. Effect of glucocorticoids on the arteries in rheumatoid arthritis. Arthritis Rheum. 2004 Dec;50(12):3813-22

236. Gubba EM, Netherton CM, Herbert J. Endangerment of the brain by glucocorticoids: experimental and clinical evidence. J Neurocytol. 2000 May-Jun;29(5-6):439-49.

237. Sholter DE, Armstrong PW. Adverse effects of corticosteroids on the cardiovascular system. Can J Cardiol. 2000 Apr;16(4):505-11

238. Allen DB. Growth suppression by glucocorticoid therapy. Endocrinol Metab Clin North Am. 1996 Sep;25(3):699-717

7. Glucocorticoid treatment: follow-up

239. 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

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?

Glucocortiocoid 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.

1. Demitrack MA, Dale JK, Straus SE, Laue L, Listwak SJ, Kruesi MJP, Chrousos G, Gold PW. Evidence for impaired activation of the hypothalamic-pituitary-adrenal axis in patients with chronic fatigue syndrome. J Clin Endocrinol Metab. 1991;73(6) :1224-34
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

3. Cleare AJ, Miell J, Heap E, Sookdeo S, Young L, Malhi GS, O'Keane V. Hypothalamo-pituitary-adrenal axis dysfunction in chronic fatigue syndrome, and the effects of low-dose hydrocortisone therapy. J Clin Endocrinol Metab 2001 Aug;86(8):3545-54 *("improvement in fatigue seen in some patients with chronic fatigue syndrome during hydrocortisone treatment is accompanied by a reversal of the blunted cortisol responses to human CRH.")*

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.

4. Swartz SL, Dluhy RG. Corticosteroids: clinical pharmacology and therapeutic use. Drugs. 1978 Sep;16(3):238-55

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. McKenzie R, O'Fallon A, Dale J, Demitrack M, Sharma G, Deloria M, Garcia-Borreguero D, Blackwelder W, Straus SE. Low-dose hydrocortisone for treatment of chronic fatigue syndrome: a randomized controlled trial. JAMA. 1998 Sep 23-30;280(12):1061-6 *("some suppression of adrenal glucocorticoid responsiveness was documented in 12 patients on 30 who received hydrocortisone compared to none in the placebo group")*
6. Demitrack MA, Dale JK, Straus SE, Laue L, Listwak SJ, Kruesi MJP, Chrousos G, Gold PW. Evidence for impaired activation of the hypothalamic-pituitary-adrenal axis in patients with chronic fatigue syndrome. J Clin Endocrinol Metab. 1991;73(6):1224-34

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 glucocortiocoids 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

8. Masharani U, Shiboski S, Eisner MD, Katz PP, Janson SL, Granger DA, Blanc PD. Impact of exogenous glucocorticoid use on salivary cortisol measurements among adults with asthma and rhinitis. Psychoneuroendocrinology. 2005 Sep;30(8):744-52

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*

has received a glucocorticoid in a dose equivalent to 20 to 30 mg/day of prednisone for more than 5 days should be suspected of having hypothalamic-pituitary suppression

9. Axelrod L. Glucocorticoid therapy. Medicine (Baltimore). 1976 Jan;55(1):39-65
10. Axelrod L. Glucocorticoids. In Kelley WN, Harris ED Jr, Ruddy S, Sledge CB (esd); Textbook of Rheumatology, ed 4. Philadelphia: Saunders, 1993
11. Daly JR, Fletcher MR, Glass D, Chambers DJ, Bitensky L, Chayen J. Comparison of effects of long-term corticotrophin and corticosteroid treatment on responses of plasma growth hormone, ACTH, and corticosteroid to hypoglycaemia. Br Med J. 1974 Jun 8;2(918):521-4.
12. Graber AL, Ney RL, Nicholson WE, Island DP, Liddle GW. Natural history of pituitary-adrenal recovery following long-term suppression with corticosteroids. J Clin Endocrinol Metab. 1965 Jan;25:11-6
13. Streck WF, Lockwood DH. Pituitary adrenal recovery following short-term suppression with corticosteroids. Am J Med. 1979 Jun;66(6):910-4 *(-50 % reduction of pituitary-adrenal axis after 5 days of 50 mg/day prednisone, full recovery in 5 days after stopping the 5-day treatment)*
14. Spitzer SA, Kaufman H, Koplovitz A, Topilsky M, Blum I. Beclomethasone dipropionate and chronic asthma. The effect of long-term aerosol administration on the hypothalamic-pituitary-adrenal axis after substitution for oral therapy with corticosteroids. Chest. 1976 Jul;70(1):38-42. *(Beclomethasone dipropionate aerosol therapy permitted in patients who had previously received prolonged treatment with corticosteroids with various degrees of adrenal suppression to achieve almost complete recovery of adrenal function within a period of six months in most patients; treatment with beclomethasone dipropionate did not affect the hypothalamic-pituitary-adrenal axis in other asthmatic patients who had not received prolonged corticosteroid therapy)*
15. Westerhof L, van Ditmars MJ, Kinderen PJ der, Thijssen JH, Schwarz F. Recovery of adrenocortical function during long-term treatment with corticosteroids. Br Med J. 1970 Nov 28;4(734):534-7
16. Westerhof L, Van Ditmars MJ, Der Kinderen PJ, Thijssen JH, Schwarz F. Recovery of adrenocortical function during long-term treatment with corticosteroids. Br Med J. 1972 Apr 22;2(807):195-7

Suprareplacement/pharmacological doses in severe critical illnesses, high doses may be used but these doses usually suppress adrenal function. After long-term use of very high doses the adrenal cortex secretions may almost totally be suppressed. To completely block endogenous production minimal doses of 15 mg per day of prednisolone or 75 or more of hydrocortisone ar necessary, but in some patients much higher doses have to be reached before completely blocking the adrenal glands. Without external stimulation, it can take an average of eight to twelve months to fully recover the initial adrenal axis as have been shown in patients who had removal of adrenal tumors that were hypersecreting cortisol.

Pharmacological doses are doses above 7.5 mg/day of prednisone

17. Hermus AR, Zelissen 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 mineralocorticoids. 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)*

It is important to note that even in the case high doses (from 20 to 50 mg/d) of a synthetic derivative as prednisone (apparently more suppressive than the natural one), the inhibition of the corticotrope axis is temporary and partia

18. Bartelink AK, van Deuren M, Hermus AR, Gemke RJ, Thijs LG. Corticosteroid administration for critically ill patients. Ned Tijdschr Geneeskd. 2001 Sep 8;145(36):1725-9
19. Kuperman H, Damiani D, Chrousos GP, Dichtchekenian V, Manna TD, Filho VO, Setian N. Evaluation of the hypothalamic-pituitary-adrenal axis in children with leukaemia before and after 6 weeks of high-dose glucocorticoid therapy. J Clin Endocrinol Metab. 2001 Jul;86(7):2993-6.
20. Wenning GK, Wietholter H, Schnauder G, Muller PH, Kanduth S, Renn W. Recovery of the hypothalamic-pituitary-adrenal axis from suppression byshort-term, high-dose intravenous prednisolone therapy in patients with MS. Acta Neurol Scand. 1994 Apr;89(4):270-3.
21. Moore GE, Hoenig M. Duration of pituitary and adrenocortical suppression after long-term administration of anti-inflammatory doses of prednisone in dogs. Am J Vet Res. 1992 May;53(5):716-20.
22. Rubens R. Corticoid therapy: how? Bull Soc Belge Ophtalmol. 1990;236:45-55.
23. Karitzky D, von Petrykowski W, Bohlayer R, Zeisel H. Recovery of hypothalamic-pituitary-adrenocortical axis after high-dose dexamethasone treatment. Dtsch Med Wochenschr. 1980 Aug 1;105(31):1086-9.
24. Streck WF, Lockwood DH. Pituitary adrenal recovery following short-term suppression with corticosteroids. Am J Med. 1979 Jun;66(6):910-4

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*

25. Kelestimur F, Akgun A, Gunay O. A comparison between short synacthen test and depot synacthen test in the evaluation of cortisol reserve of adrenal gland in normal subjects. J Endocrinol Invest. 1995 Dec;18(11):823-6
26. Oberger E, Thoren M, Engstrom I. Long-term treatment with corticosteroids/ACTH in asthmatic children. II. Hypothalamic-pituitary-adrenal function. Acta Paediatr Scand. 1986 Jan;75(1):164-71
27. Hugh-Jones P, Pearson RS, Booth M. Tetracosactrin for the management of asthmatic patients after long-term corticosteroids. Thorax. 1975 Aug;30(4):426-9
28. Obtulowicz K, Glowacka A. Synacthen-depot treatment during withdrawal of long-term corticotherapy in patients with asthma. Pol Tyg Lek. 1974 Apr 1;29(13):519-22

2. <u>Can treatment with hydrocortisone or glucocorticoids reduce bone density?</u>

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")*

<u>Studies with adverse effects of glucocortioid treatment on bone density</u>:

Study where persons with higher peak serum level of cortisol after ACTH stimulation have an increased bone density loss

2. Reynolds RM, Dennison EM, Walker BR, Syddall HE, Wood PJ, Andrew R, Phillips DI, Cooper C. Cortisol secretion and rate of bone loss in a population-based cohort of elderly men and women. Calcif Tissue Int. 2005 Sep;77(3):134-8 *(increased lumbar spine bone loss in men, reduced femoral neck bone density in women)*

Studies where the use of glucocortioids 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)*
4. Krogsgaard MR, Thamsborg G, Lund B.[Bone loss during low dose glucocorticoid treatment in patients with polymyalgia rheumatica. A double-blind, prospective comparison between prednisolone and deflazacort. Ugeskr Laeger. 1997 Jul 21;159(30):4641-4
5. McKenzie R, Reynolds JC, O'Fallon A, Dale J, Deloria M, Blackwelder W, Straus SE. Decreased bone mineral density during 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)*
6. Sambrook PN, Eisman JA, Champion GD, Pocock NA. Sex hormone status and osteoporosis in postmenopausal women with rheumatoid arthritis. Arthritis Rheum. 1988 Aug;31(8):973-8 *(8.2 mg of prednisone alone causes reduces significantly the bone density of the lumbar spine, not of the femoral neck)*
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)*

<u>Studies with no effect of glucocortioid treatment on bone density</u>: 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")*
10. van Everdingen AA, Siewertsz van Reesema DR, Jacobs JW, Bijlsma JW. Low-dose glucocorticoids in early rheumatoid arthritis: discordant effects on bone mineral density and fractures? Clin Exp Rheumatol. 2003 Mar-Apr;21(2):155-60 *(No significant effect on bone density, but a non significant increase in vertebral fractures)*

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

11. 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

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

12. Wichers M, Springer W, Bidlingmaier F, Klingmuller D. How hydrocortisone substitution influences the quality of life and the bone metabolism of patients with secondary hypocortisolism. Eur J Clin Invest 2000 Dec;30 Suppl 3:55-7

Studies with beneficial effect of glucocorticoid treatment on bones

Beneficial effect of prednisolone on bone density in rheumatoid arthritis

13. Haugeberg G, Strand A; Kvien TK, Kirwan JR. 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

Beneficial effect of cortisol against bone resortion in vitro

14. Krieger NS, Frick KK, Bushinsky DA. Cortisol inhibits acid-induced bone resorption in vitro. J Am Soc Nephrol. 2002 Oct;13(10):2534-9
15. Sandberg AL, Raisz LG, Wahl LM, Simmons HA. Enhancement of complement-mediated prostaglandin synthesis and bone resorption by arachidonic acid and inhibition by cortisol. Prostaglandins Leukot Med. 1982 May;8(5):419-27
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

17. Kotaniemi A, Piirainen H, Paimela L, Leirisalo-Repo M, Uoti-Reilama K, Lahdentausta P, Ruotsalainen P, Kataja M, Vaisanen E, Kurki P. Is continuous intranasal salmon calcitonin effective in treating axial bone loss in patients with active rheumatoid arthritis receiving low dose glucocorticoid therapy? J Rheumatol. 1996 Nov;23(11):1875-9 *(calcitonin-users increased in bone density, while the non-calcitonin users decreased in bone density)*
18. Sambrook P, Birmingham J, Kelly P, Kempler S, Nguyen T, Pocock N, Eisman J. Prevention of corticosteroid bone loss. Osteoporos Int. 1993;3 Suppl 1:141-3.
19. Sambrook P, Birmingham J, Kelly P, Kempler S, Nguyen T, Pocock N, Eisman J. Prevention of corticosteroid osteoporosis. A comparison of calcium, calcitriol, and calcitonin. N Engl J Med. 1993 Jun 17;328(24):1747-52
20. Kapetanakis EI, Antonopoulos AS, Antoniou TA, Theodoraki KA, Zarkalis DA, Sfirakis PD, Chilidou DA, Alivizatos PA. Effect of long-term calcitonin administration on steroid-induced osteoporosis after cardiac transplantation. J Heart Lung Transplant. 2005 May;24(5):526-32.
21. Cappio F, Colombo MD, Caputo R. of salmon calcitonin nasal spray in the prevention of corticosteroid-induced osteoporosis in bullous diseases. G Ital Dermatol Venereol. 1990 Dec;125(12):LXI-LXIV

With female hormone replacement

22. Sambrook P, Birmingham J, Champion D, Kelly P, Kempler S, Freund J, Eisman J. Postmenopausal bone loss in rheumatoid arthritis: effect of estrogens and androgens. J Rheumatol. 1992 Mar;19(3):357-61. *(female HRT was efficient to block any excess bone loss that 7.5mg/day of prednisolone caused in the HRT-untreated patients during 0.9 yrs)*

With GH

23. Kovacs G, Fine RN, Worgall S, Schaefer F, Hunziker EB, Skottner-Lindun A, Mehls O. Growth hormone prevents steroid-induced growth depression in health and uremia. Kidney Int. 1991 Dec;40(6):1032-40.

24. Giustina A, Bussi AR, Jacobello C, Wehrenberg WB. Effects of recombinant human growth hormone (GH) on bone and intermediary metabolism in patients receiving chronic glucocorticoid treatment with suppressed endogenous GH response to GH-releasing hormone. J Clin Endocrinol Metab. 1995 Jan;80(1):122-9. *(In patients receiving chronic glucocorticoid treatment, GH administration may significantly antagonize several side-effects of long term glucocorticoid administration, such as protein wasting, osteoporosis, and hyperlipidemia, and T-helper/T-suppressor cell ratio)*

25. Oehri M, Ninnis R, Girard J, Frey FJ, Keller U. Effects of growth hormone and IGF-I on glucocorticoid-induced protein catabolism in humans. Am J Physiol. 1996 Apr;270(4 Pt 1):E552-8. *(GH blocked the catabolic effects of glucocorticoids on protein metabolism)*

With vitamin D

26. Schacht E. Rationale for treatment of involutional osteoporosis in women and for prevention and treatment of corticosteroid-induced osteoporosis with alfacalcidol. Calcif Tissue Int. 1999 Oct;65(4):317-27
27. Sambrook P, Birmingham J, Kelly P, Kempler S, Nguyen T, Pocock N, Eisman J. Prevention of corticosteroid bone loss. Osteoporos Int. 1993;3 Suppl 1:141-3.

With biphosphonates

28. Reid DM, Hughes RA, Laan RF, Sacco-Gibson NA, Wenderoth DH, Adami S, Eusebio RA, Devogelaer JP. Efficacy and safety of daily risedronate in the treatment of corticosteroid-induced osteoporosis in men and women: a randomized trial. European Corticosteroid-Induced Osteoporosis Treatment Study. J Bone Miner Res. 2000 Jun;15(6):1006-13
29. Cohen S, Levy RM, Keller M, Boling E, Emkey RD, Greenwald M, Zizic TM, Wallach S, Sewell KL, Lukert BP, Axelrod DW, Chines AA. Risedronate therapy prevents corticosteroid-induced bone loss: a twelve-month, multicenter, randomized, double-blind, placebo-controlled, parallel-group study. Arthritis Rheum. 1999 Nov;42(11):2309-18
30. Jenkins EA, Walker-Bone KE, Wood A, McCrae FC, Cooper C, Cawley MI. The prevention of corticosteroid-induced bone loss with intermittent cyclical etidronate. Scand J Rheumatol. 1999;28(3):152-6
31. Homik JE, Cranney A, Shea B, Tugwell P, Wells G, Adachi JD, Suarez-Almazor ME. A metaanalysis on the use of bisphosphonates in corticosteroid induced osteoporosis. J Rheumatol. 1999 May;26(5):1148-57
32. Roux C, Oriente P, Laan R, Hughes RA, Ittner J, Goemaere S, Di Munno O, Pouilles JM, Horlait S, Cortet B. Randomized trial of effect of cyclical etidronate in the prevention of corticosteroid-induced bone loss. Ciblos Study Group. J Clin Endocrinol Metab. 1998 Apr;83(4):1128-33

With sodium floride

33. Lems WF, Jacobs WG, Bijlsma JW, Croone A, Haanen HC, Houben HH, Gerrits MI, van Rijn HJ. Effect of sodium fluoride on the prevention of corticosteroid-induced osteoporosis. Osteoporos Int. 1997;7(6):575-82

Exercise

34. Braith RW, Mills RM, Welsch MA, Keller JW, Pollock ML. Resistance exercise training restores bone mineral density in heart transplant recipients. J Am Coll Cardiol. 1996 Nov 15;28(6):1471-7
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, Bleasel 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

120. Chen H, Sun S, Mei Y, Liu C, Liu A, Tong E. The effect of beta-amyloid on neurons and the influence of glucocorticoid and age on such effect. J Huazhong Univ Sci Technolog Med Sci. 2002;22(3):250-2
121. Keenan PA, Jacobson MW, Soleymani RM, Mayes MD, Stress ME, Yaldoo DT. The effect on memory of chronic prednisone treatment in patients with systemic disease. Neurology. 1996 Dec;47(6):1396-402.

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

No effect of glucocorticoids in Alzhiemer's disease

122. Aisen PS, Davis KL, Berg JD, Schafer K, Campbell K, Thomas RG, Weiner MF, Farlow MR, Sano M, Grundman M, Thal LJ. A randomized controlled trial of prednisone in Alzheimer's disease. Alzheimer's Disease Cooperative Study. Neurology. 2000 Feb 8;54(3):588-93.

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

Reduced glucocorticoid response in Alzheimer's disease

123. Linder J, Nolgard P, Nasman B, Back O, Uddhammar A, Olsson T. Decreased peripheral glucocorticoid sensitivity in Alzheimer's disease. Gerontology. 1993;39(4):200-6

Glucocorticoid treatment improves the memory for stressful events or avoidance reactions

124. Peeters BW, Broekkamp CL. Involvement of corticosteroids in the processing of stressful life-events. A possible implication for the development of depression. J Steroid Biochem Mol Biol. 1994 Jun;49(4-6):417-27.
125. Sandi C, Rose SP, Mileusnic R, Lancashire C. Corticosterone facilitates long-term memory formation via enhanced glycoprotein synthesis. Neuroscience. 1995 Dec;69(4):1087-93
126. Roozendaal B, Carmi O, McGaugh JL. Adrenocortical suppression blocks the memory-enhancing effects of amphetamine and epinephrine. Proc Natl Acad Sci U S A. 1996 Feb 20;93(4):1429-33
127. Roozendaal B, McGaugh JL. The memory-modulatory effects of glucocorticoids depend on an intact stria terminalis. Brain Res. 1996 Feb 19;709(2):243-50
128. Roozendaal B, McGaugh JL. Amygdaloid nuclei lesions differentially affect glucocorticoid-induced memory enhancement in an inhibitory avoidance task. Neurobiol Learn Mem. 1996 Jan;65(1):1-8

Anecdotal report on dementia reversed with glucocorticoid treatment

129. Basavaraju N, Phillips SL. Cortisol deficient state. A cause of reversible cognitive impairment and delirium in the elderly.J Am Geriatr Soc. 1989 Jan;37(1):49-51