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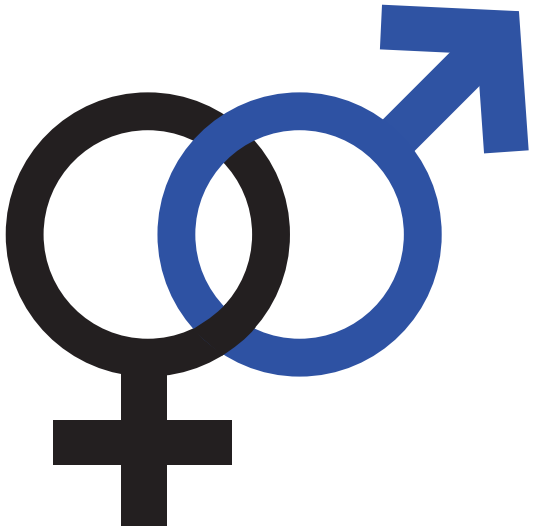
Bioidentical Hormone Abstracts for Men



Women's International Pharmacy compiled abstracts of the most up to date scientific literature on biologically identical hormones for female hormonal health concerns. To obtain the full-text of any of the abstracts listed, please refer to your local medical library or online source.

Phone: 800-279-5708 ~ Fax: 800-279-8011
Web: www.womensinternational.com ~ Email: info@womensinternational.com

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Testosterone

Bone

J Clin Endocrinol Metab. 2006; 91 (10): 3908-3915.

Association of Testosterone and Estradiol Deficiency with Osteoporosis and Rapid Bone Loss in Older Men.

Fink H, et al

Context: The clinical value of measuring testosterone and estradiol in older men with osteoporosis and of measuring bone mineral density (BMD) in older men with testosterone or estradiol deficiency is uncertain.
Objective: The objective of the study was to examine the association of testosterone and estradiol deficiency with osteoporosis and rapid bone loss in older men.
Design: This study was a cross-sectional and longitudinal analysis.
Setting: The study was conducted at six U.S. centers of the Osteoporotic Fractures in Men study.
Participants: The study population consisted of 2447 community dwelling men aged 65 yr or older.
Main Outcome Measures: Total testosterone deficiency was defined as less than 200 ng/dl. Total estradiol deficiency was defined as less than 10 pg/ml. Osteoporosis was defined as femoral neck or total hip BMD T-score of_2.5 or less. Rapid bone loss was defined as 3%/yr or more.
Results: Prevalence of osteoporosis in men with deficient and normal total testosterone was 12.3 and 6.0% (P _ 0.003) and 15.4 and 2.8% (P_0.0001) in those with deficient and normal total estradiol. Among osteoporotic men and those with normal BMD, prevalence of total testosterone deficiency was 6.9 and 3.2% (P _ 0.01), and prevalence of total estradiol deficiency was 9.2 and 2.4% (P _ 0.0001). Incidence of rapid hip bone loss in men with deficient and normal total testosterone was 22.5 and 8.6% (P _ 0.007) and in those with deficient and normal total estradiol was 14.3 and 6.3% (P _ 0.08).
Conclusions: Older men with total testosterone or estradiol deficiency were more likely to be osteoporotic. Those with osteoporosis were more likely to be total testosterone or estradiol deficient. Rapid hip bone loss was more likely in men with total testosterone deficiency. BMD testing of older men with sex steroid deficiency may be clinically warranted.

J Clin Endocrinol Metab. 2004; 89: 503-510.

Exogenous Testosterone or Testosterone with Finasteride Increases Bone Mineral Density in Older Men with Lower Serum Testosterone

Amory, JK, Watts, NB, et. al.

Older men, particularly those with low serum testosterone (T) levels, might benefit from T therapy to improve bone mineral density (BMD) and reduce fracture risk. Concerns exist, however, about the impact of T therapy on the prostate in older men. We hypothesized that the combination of T and finasteride (F), a 5 alpha-reductase inhibitor, might increase BMD in older men without adverse effects on the prostate. Seventy men aged 65 yr or older, with a serum T less than 12.1 nmol/liter on two occasions, were randomly assigned to receive one of three regimens for 36 months: T enanthate, 200 mg im every 2 wk with placebo pills daily (T-only); T enanthate, 200 mg every 2 wk with 5 mg F daily (T+F); or placebo injections and pills (placebo). Low BMD was not an inclusion criterion. We obtained serial measurements of BMD of the lumbar spine and hip by dual x-ray absorptiometry. Prostate-specific antigen (PSA) and prostate size were measured at

baseline and during treatment to assess the impact of therapy on the prostate. Fifty men completed the 36-month protocol. By an intent-to-treat analysis including all men for as long as they contributed data, T therapy for 36 months increased BMD in these men at the lumbar spine [10.2 +/- 1.4% (mean percentage increase from baseline +/- SEM; T-only) and 9.3 +/- 1.4% (T+F) vs. 1.3 +/- 1.4% for placebo ($P < 0.001$)] and in the hip [2.7 +/- 0.7% (T-only) and 2.2 +/- 0.7% (T+F) vs. -0.2 +/- 0.7% for placebo, ($P <$ or $= 0.02$)]. Significant increases in BMD were seen also in the intertrochanteric and trochanteric regions of the hip. After 6 months of therapy, urinary deoxypyridinoline (a bone-resorption marker) decreased significantly compared with baseline in both the T-only and T+F groups ($P < 0.001$) but was not significantly reduced compared with the placebo group. Over 36 months, PSA increased significantly from baseline in the T-only group ($P < 0.001$). Prostate volume increased in all groups during the 36-month treatment period, but this increase was significantly less in the T+F group compared with both the T-only and placebo groups ($P = 0.02$). These results demonstrate that T therapy in older men with low serum T increases vertebral and hip BMD over 36 months, both when administered alone and when combined with F. This finding suggests that dihydrotestosterone is not essential for the beneficial effects of T on BMD in men. In addition, the concomitant administration of F with T appears to attenuate the impact of T therapy on prostate size and PSA and might reduce the chance of benign prostatic hypertrophy or other prostate-related complications in older men on T therapy. These findings have important implications for the prevention and treatment of osteoporosis in older men with low T levels.

J Clin Endocrinol Metab. 2004; 89: 503-510.

Effects of Testosterone Replacement in Hypogonadal Men

Synder, PJ, Peachey, H, et al.

Treatment of hypogonadal men with testosterone has been shown to ameliorate the effects of testosterone deficiency on bone, muscle, erythropoiesis, and the prostate. Most previous studies, however, have employed somewhat pharmacological doses of testosterone esters, which could result in exaggerated effects, and/or have been of relatively short duration or employed previously treated men, which could result in dampened effects. The goal of this study was to determine the magnitude and time course of the effects of physiological testosterone replacement for 3 yr on bone density, muscle mass and strength, erythropoiesis, prostate volume, energy, sexual function, and lipids in previously untreated hypogonadal men. We selected 18 men who were hypogonadal (mean serum testosterone +/- SD, 78 +/- 77 ng/dL; 2.7 +/- 2.7 nmol/L) due to organic disease and had never previously been treated for hypogonadism. We treated them with testosterone transdermally for 3 yr. Sixteen men completed 12 months of the protocol, and 14 men completed 36 months. The mean serum testosterone concentration reached the normal range by 3 months of treatment and remained there for the duration of treatment. Bone mineral density of the lumbar spine (L2-L4) increased by 7.7 +/- 7.6% ($P < 0.001$), and that of the femoral trochanter increased by 4.0 +/- 5.4% ($P = 0.02$); both reached maximum values by 24 months. Fat-free mass increased 3.1 kg ($P = 0.004$), and fat-free mass of the arms and legs individually increased, principally within the first 6 months. The decrease in fat mass was not statistically significant. Strength of knee flexion and extension did not change. Hematocrit increased dramatically, from mildly anemic (38.0 +/- 3.0%) to midnormal (43.1 +/- 4.0%; $P = 0.002$) within 3 months, and remained at that level for the duration of treatment. Prostate volume also increased dramatically, from subnormal (12.0 +/- 6.0 mL) before treatment to normal (22.4 +/- 8.4 mL; $P = 0.004$), principally during the first 6 months. Self-reported sense of energy (49 +/- 19% to 66 +/- 24%; $P = 0.01$) and sexual function (24 +/- 20% to 66 +/- 24%; $P < 0.001$) also increased, principally within the first 3 months. Lipids did not change. We conclude from this study that replacing testosterone in hypogonadal men increases bone mineral density of the spine and hip, fat-free mass, prostate volume, erythropoiesis, energy, and sexual function. The full effect of testosterone on bone mineral density took 24 months, but the full effects on the other tissues took only 3-6 months.

These results provide the basis for monitoring the magnitude and the time course of the effects of testosterone replacement in hypogonadal men.

Cardiovascular

Euro Heart Journal. 2006 Jan; 27 (1): 57-64.

Testosterone therapy in men with moderate severity heart failure: a double blind randomized placebo controlled trial

Malkin C, Pugh P, West J, et al.

Aims: Chronic heart failure is associated with maladaptive and prolonged neurohormonal and proinflammatory cytokine activation causing a metabolic shift favouring catabolism, vasodilator incapacity, and loss of skeletal muscle bulk and function. In men, androgens are important determinants of anabolic function and physical strength and also possess anti-inflammatory and vasodilatory properties.
Methods and Results: We conducted a randomized, double-blind, placebo-controlled parallel trial of testosterone replacement therapy (5 mg Androderm) at physiological doses in 76 men (mean+SD, age 64+9.9) with heart failure (ejection fraction 32.5+11%) over a maximum follow-up period of 12 months. The primary endpoint was functional capacity as assessed by the incremental shuttle walk test (ISWT). At baseline, 18 (24%) had serum testosterone below the normal range and bioavailable testosterone correlated with distance walked on the initial ISWT (r ¼ 0.3, P ¼ 0.01). Exercise capacity significantly improved with testosterone therapy compared with placebo over the full study period (mean change þ25+15 m) corresponding to a 15+11% improvement from baseline (P ¼ 0.006 ANOVA). Symptoms improved by at least one functional class on testosterone in 13 (35%) vs. 3 (8%) on placebo (P ¼ 0.01). No significant changes were found in handgrip strength, skeletal muscle bulk by cross-sectional computed tomography, or in tumour necrosis factor levels. Testosterone therapy was safe with no excess of adverse events although the patch preparation was not well tolerated by the study patients.
Conclusion: Testosterone replacement therapy improves functional capacity and symptoms in men with moderately severe heart failure.

Euro Heart Journal. 2003; 24: 909-915.

Acute haemodynamic effects of testosterone in men with chronic heart failure

Pugh P, Jones TH, Channer KS

Aims: Anabolic therapy with testosterone may be useful in the treatment of wasting associated with chronic heart failure but little is known about its cardiovascular actions. The aim of this study was to determine the acute haemodynamic effects of testosterone administration in men with heart failure.
Methods and results: Twelve men with stable chronic heart failure were enrolled in a double-blind, randomised, placebo-controlled, cross-over trial. Subjects were given testosterone 60 mg or placebo via the buccal route and central haemodynamics were monitored over 6 h, using a pulmonary flotation catheter. Subjects received the second treatment on day 2 and haemodynamic monitoring was repeated. Treatment was well tolerated. Compared with placebo, testosterone treatment resulted in a relative increase in cardiac output ($p<0.0001$, ANCOVA), with maximum treatment effect after 180 min (10.3±4.6% increase from baseline, p□0.035; 95% CI 0.8–19.8). This was accompanied by reduction in systemic vascular resistance compared with baseline ($p<0.0001$, ANCOVA), with maximum treatment effect also at 180 min (−17.4±9.6% from

baseline, p□0.085; 95% CI −37.3 to +2.6). These maximal changes coincided with the peak elevation in serum bio-available testosterone. There was no significant change in any other haemodynamic parameter measured.
Conclusions: Administration of testosterone increases cardiac output acutely, apparently via reduction of left ventricular afterload.

Diabetes

Diabetes Care. 2007; 30: 234-238.

Androgens and Diabetes in Men: Results from the Third National Health and Nutrition Examination Survey (NHANES III).

Selvin E., Feinleib, M., et al.

Objective: Low levels of androgens in men may play a role in the development of diabetes; however, few studies have examined the association between androgen concentration and diabetes in men in the general population. The objective of this study is to test the hypothesis that low normal levels of total, free, and bioavailable testosterone are associated with prevalent diabetes in men.
Research Design and Methods: The study sample included 1,413 adult men aged ≥20 years who participated in the morning session of the first phase of the Third National Health and Nutrition Examination Survey, a cross-sectional survey of the civilian, noninstitutionalized population of the U.S. Bioavailable and free testosterone levels were calculated from serum total testosterone, sex hormone binding globulin, and albumin concentrations.
Results: In multivariable models adjusted for age, race/ethnicity, and adiposity, men in the first tertile (lowest) of free testosterone level were four times more likely to have prevalent diabetes compared with men in the third tertile (odds ratio 4.12 {95% CI 1.25-13.55}). Similarly, men in the first tertile of bioavailable testosterone also were approximately four times as likely to have prevalent diabetes compared with men in the third tertile (3.93 {1.39-11.13}). These associations persisted even after excluding men with clinically abnormal testosterone concentrations defined as total testosterone <3.25 ng/ml or free testosterone <0.07 ng/ml. No clear association was observed for total testosterone after multivariable adjustment (P for trend across tertiles = 0.27).
Conclusions: Low free and bioavailable testosterone concentrations in the normal range were associated with diabetes, independent of adiposity. These suggest that low androgen levels may be a risk factor for diabetes in men.

Erectile Dysfunction

BJU International. 2007; 99: 988-992.

Effects of testosterone on erectile function: implications for the therapy of erectile dysfunction.

Saad. F., Grahl, A.S., et al.

Sexual potency declines with age, as does the efficiency of erection. Many studies show that different patterns of erectile dysfunction (ED), varying from occasional inability to obtain a full erection, impairment throughout intercourse and total absence of erectile response, might not be triggered by psychological factors only. Recent research indicates that ED relies on organic causes, and has challenged the development of new therapies. One therapeutic approach in patients who have testosterone deficiency is based on androgen therapy. Thus, we reviewed data

on testosterone-induced effects relative to erectile function, summarizing the results from studies reported in 1991-2006 on testosterone therapy in patients with ED and hypogonadism, with a special focus on men not responding to phosphodiesterase-5 (PDE-%) inhibitors. We searched several computerized databases parallel with printed bibliographic references. Many studies have established animal models, which confirm that testosterone is important in modulating the central and peripheral regulation of ED. Testosterone deprivation has a strong negative impact on the structure of penile tissues and erectile nerves, which can be prevented by androgen administration. Combined therapy regimens with PDE-5 inhibitors and testosterone might improve ED in patients with hypogonadism of different causes. Thus, androgen treatment in hypogonadic patients, including those unresponsive to PDE-5 inhibitors, often results in an improvement of ED. Testosterone therapy is sage and convenient, while rapidly correcting low testosterone levels.

General

Arch Gen Psychiatry. 2008; 65(3): 283-289.

Low Free Testosterone Concentration as a Potentially Treatable Cause of Depressive Symptoms in Older Men

Almeida OP, Yeap BB, Hankey GJ, et al.

Context: Serum conentrations of gonadal hormones have been associated with various measure of wellbeing, but it is unclear whether their association with mood is confounded by concurrent physical morbidity.
Objective: To determine whether the association between serum testosterone concentration and mood in older men is independent of physical comorbidity.
Results: Of 3987 men included in the study, 203 (5.1%; 95 confidence interval [CI], 4.4%-5.8%) had depression. Participants with depressin had significantly lower total and free testosterone concentrations than nondepressed men (P<.001). however, they were also more likely to smoke and to have low educational attainment, a body mass index categorized as obese, a Mini-Mental State Examination sore less than 24, a history of antidepressant drug treatemtn, and greater concurrent physical morbidity. After adjusting for these factors and for age, men with depression were 1.55 (95% CI, 0.91-2.63) and 2.71 (95% CI, 1.49-4.93) times more likely to have total and free testosterone concentrations, respectively, in the lowest quintile.
Conclusions: A free testosterone concentration in the lowest quintile is associated with a higher prevalence of depression, and this association cannot be adequately explained by physical comorbidity. A randomized controlled trial is required to determine whether the link between low free testosterone levels and depression is causal because older men with depression may benefit from systemic screening of free testosterone concentration and testosterone supplementation.

Aging Male. 2007; 10 (3): 139-153.

Testosterone therapy in the aging male.

Lunenfeld, B., Nieschlag, E.

The decline, with aging, in serum concentrations of biologically active forms of testosterone in men is an indisputable fact and some men will eventually develop symptoms of late-onset hypogonadism (LOH) with its clinical consequences. LOH reduces quality of life and may pose important risk factors for frailty, changes in body composition, cardiovascular disease, sexual dysfunction and osteoporosis. Testosterone supplementation in cases of LOH will restore serum testosterone levels into the physiologic range; will restore metabolic parameters to the eugondal state, increase muscle mass, strength, and function; maintain or improve BMD reducing fracture risk; will improve neuropsychological function (cognition and mood); quality of life; to reduce disability, to compress major illness into a narrow age range and to add life to years. To achieve

these goals men must also adjust their lifestyle to optimize dietary habits, as well as to exercise and to abstain from smoking life-long. Monitoring these patients is a shared responsibility that cannot be taken lightly. The physician must emphasize to the patient the need for periodic evaluation and the patient must agree to comply with these requirements. The physician's evaluation should include an assessment of the clinical response and monitoring must be tailored to the indications and individual needs of the patient.
Results: Seven male and 2 female patients, seen between July 2004 and February 2005, and between the ages of 32 and 56, are reported with histories of treatment resistant cluster headaches accompanied by borderline low or low serum testosterone levels. The patients failed to respond to individually tailored medical regimens, including melatonin doses of 12 mg a day or higher, high flow oxygen, maximally tolerated verapamil, antiepileptic agents, and parenteral serotonin agonists. Seven of the 9 patients met 2004 International Classification for the Diagnosis of Headache criteria for chronic cluster headaches; the other 2 patients had episodic cluster headaches of several months duration. After neurological and physical examination all patients had laboratory investigations including fasting lipid panel, PSA (where indicated), LH, FSH, and testosterone levels (both free and total). All 9 patients demonstrated either abnormally low or low, normal testosterone levels. After supplementation with either pure testosterone in 5 of 7 male patients or combination testosterone/estrogen therapy in both female patients, the patients achieved cluster headache freedom for the first 24 hours. Four male chronic cluster patients, all with abnormally low testosterone levels, achieved remission.
Conclusions: Abnormal testosterone levels in patients with episodic or chronic cluster headaches refractory to maximal medical management may predict a therapeutic response to testosterone replacement therapy. In the described cases, diurnal variation of attacks, a seasonal cluster pattern, and previous, transient responsiveness to melatonin therapy pointed to the hypothalamus as the site of neurological dysfunction. Prospective studies pairing hormone levels and polysomnographic data are needed.

J Clin Endocrinol & Metab. 2000; 85: 2839-2853.

Transdermal Testosterone Gel Improves Sexual Function, Mood, Muscle Strength, and Body Composition Parameters in Hypogonadal Men

Wang C, Swerdloff RS, Iranmanesh A, et al.

Testosterone (T) therapy for hypogonadal men should correct the clinical abnormalities of T deficiency, including improvement of sexual dysfunction, increase in muscle mass and strength, and decrease in fat mass, with minimal adverse effects. We have shown that administration of a new transdermal T gel formulation to hypogonadal men provided dose proportional increases in serum T levels to the normal adult male range. We now reports the effects of 180 days of treatment with this 1% T gel preparation (50 or 100mg/day, contained in 5 or 10 g gel, respectively) compared to those of a permeation-enhanced T patch (5 mg/day) on defined efficacy parameters in 227 hypogonadal men. In the T gel groups, the T dose was adjusted up or down to 75 mg/day (contained in 7.5 g gel) on day 90 if serum T concentrations were below or above the normal male range. No dose adjustment was made with the T patch group. Sexual function and mood changes were monitored by questionnaire, body composition was determined by dual energy x-ray absortiometry, and muscle strength was measured by the one repetitive maximum technique on bench and leg perss exercises. Sexual function and mood improced maximally on day 30 of treatment, without differences across groups, and showed no further improvement with continuation of treatment. Mena muscle strength in the leg press exercise increased by 11 to 13 kg in all treatment groups by 90 days and did not improve further at 180 days of treatment. Moderate increases were also observed in arm/chest muscle strength. At 90 days of treatment, lean body mass increased more in the 100mg/day T gel group (2.74 ± 0.28 kg; P=0.0002) than in the 50 mg/day T gel (1.28 ± 0.32 kg) and T patch groups (1.20 ± 0.26 kg). fat mass and percent fat were not significantly decreased in the T patch group, but showed decreases in the T gel groups (50

mg/day , -0.90 ± 0.32 kg; 100 mg/day, -1.05 ± 0.22 kg). the increase in lean mass and the decrease in fat mass were correlated with the changes in average serum T levels attained after transdermal T replacement. These beneficial effects of T replacement were accompanied by the anticipated increases in hematocrit and hemoglobin but without significant changes in the lipid profile. The increase in mean serum prostate-specific antigen levels (within the normal range) was correlated with serum levels of T. The greatest increases were noted in the 100 mg/day T gel group. Skin irritation was reported in 5.5% of subjects treated with T gel and in 66% of subjects in the permeation-enhanced T patch group. We conclude that T gel replacement improved sexual function and mood, increased lean mass and muscle strength (principally in the legs) and decreased fat mass in hypogonadal men with less skin irritation and discontinuation compared with the recommended dose of the permeation-enhanced T patch.

Metabolic Syndrome

Arch Gen Psychiatry. 2008; 65(3): 283-289.

Low Free Testosterone Concentration as a Potentially Treatable Cause of Depressive Symptoms in Older Men

Almeida OP, Yeap BB, Hankey GJ, et al.

Context: Serum concentrations of gonadal hormones have been associated with various measures of wellbeing, but it is unclear whether their association with mood is confounded by concurrent physical morbidity.
Objective: To determine whether the association between serum testosterone concentration and mood in older men is independent of physical comorbidity.
Main Outcome Measures: We used the 15 item Geriatric Depression Scale (GDS-15) to assess depressed mood. Clinically significant depression was defined a priori as a GDS-15 score of 7 or greater. Physical health was assessed using the weighted Carlson index and the Physical Component Summary score of the 36-Item Short Form Health Survey.
Results: Of 3987 men included in the study, 203 (5.1%; 95% confidence interval [CI], 4.4%-5.8%) had depression. Participants with depression had significantly lower total and free testosterone concentrations than nondepressed men (P<.001 for both). However, they were also more likely to smoke and to have low educational attainment, a body mass index categorized as obese, a Mini-Mental State Examination score less than 24, a history of antidepressant drugs treatment , and greater concurrent physical morbidity. After adjusting for these factors and for age, men with depression were 1.55 (95% CI, 0.91-2.63) and 2.71 (95% CI, 1.49-4.93) times more likely to have total and free testosterone concentrations, respectively, in the lowest quintile.
Conclusions: A free testosterone concentration in the lowest quintile is associated with a higher prevalence of depression, and this association cannot be adequately explained by physical comorbidity. A randomized controlled trial is required to determine whether the link between low free testosterone level and depression is causal because older men with depression may benefit from systematic screening of free testosterone concentration and testosterone supplementation.

J Clin Endocrinol Metab. 2007; 92 (9): 3568-3572.

Aging, androgens, and the metabolic syndrome in a longitudinal study of aging.

Rodriguez, A., Muller, D.C., et al.

BACKGROUND: Based on Adult Treatment Panel III criteria, we previously reported that the prevalence of the metabolic syndrome (MS) increased with aging; was higher if elevated 2-h plasma postglucose challenge values were included as a criterion; and was greater in men, compared with women. The aim of this study was to evaluate the relationship between the MS and

circulating androgen levels in a cohort of men in the Baltimore Longitudinal Study of Aging.
METHODS AND RESULTS: Study participants were Caucasian community-dwelling adult men in the Baltimore Longitudinal Study of Aging, who underwent a fasting 2-h oral glucose tolerance test and had serum concentrations of total testosterone (T), dehydroepiandrosterone sulfate, and SHBG levels measured. The prevalence of the MS was 4, 21, 21, and 18% for men between the ages of 20 and 39, 40 and 59, 60 and 79, and 80 and 94 yr, respectively. Total T and SHBG were inversely related to the development of the MS over a mean follow-up period of 5.8 yr (range 1.5-14.0 yr), whereas the free T index and body mass index were positively related to the incidence of the MS. Age alone did not predict the development of the MS, nor did the inclusion of abnormal 2-h plasma postglucose challenge levels in the classification of the MS. Stepwise proportional hazards regression analyses showed that among the various measurements, SHBG levels exerted the greatest influence on development of the MS.
CONCLUSION: The prevalence of the MS increased with aging, and this was associated with lower androgen levels. Lower total T and SHBG predicted a higher incidence of the MS.

Euro J Endocrinol. 2006; 154: 899-906.

Testosterone replacement therapy improves insulin resistance, glycaemic control, visceral adiposity and hypercholesteraemia in hypogonadal men with type 2 diabetes.

Kapoor D, et al.

Objective: Low levels of testosterone in men have been shown to be associated with type 2 diabetes, visceral adiposity, dyslipidaemia and metabolic syndrome. We investigated the effect of testosterone treatment on insulin resistance and glycaemic control in hypogonadal men with type 2 diabetes. Design: This was a double-blind placebo-controlled crossover study in 24 hypogonadal men (10 treated with insulin) over the age of 30 years with type 2 diabetes.
Methods: Patients were treated with i.m. testosterone 200 mg every 2 weeks or placebo for 3 months in random order, followed by a washout period of 1 month before the alternate treatment phase. The primary outcomes were changes in fasting insulin sensitivity (as measured by homeostatic model index (HOMA) in those not on insulin), fasting blood glucose and glycated haemoglobin. The secondary outcomes were changes in body composition, fasting lipids and blood pressure. Statistical analysis was performed on the delta values, with the treatment effect of placebo compared against the treatment effect of testosterone. Results: Testosterone therapy reduced the HOMA index (K1.73G0.67, PZ0.02, nZ14), indicating an improved fasting insulin sensitivity. Glycated haemoglobin was also reduced (K0.37G0.17%, PZ0.03), as was the fasting blood glucose (K1.58G0.68 mmol/l, PZ0.03). Testosterone treatment resulted in a reduction in visceral adiposity as assessed by waist circumference (K1.63G0.71 cm, PZ0.03) and waist/hip ratio (K0.03G0.01, PZ0.01). Total cholesterol decreased with testosterone therapy (K0.4G0.17 mmol/l, PZ0.03) but no effect on blood pressure was observed.
Conclusions: Testosterone replacement therapy reduces insulin resistance and improves glycaemic control in hypogonadal men with type 2 diabetes. Improvements in glycaemic control, insulin resistance, cholesterol and visceral adiposity together represent an overall reduction in cardiovascular risk.

The Journal of Urology. 2005 September; 174: 827-834.

Hypogonadism and Metabolic Syndrome: Implications for Testosterone Therapy

Makhsida N, Shah J, Yan G, Fisch H, Shabsigh R

Purpose: Metabolic syndrome, characterized by central obesity, insulin resistance, dyslipidemia and hypertension, is highly prevalent in the United States. When left untreated, it significantly increases the risk of diabetes mellitus and cardiovascular disease. It has been suggested that hypogonadism may be an additional component of metabolic syndrome. This has potential implications for the treatment of metabolic syndrome with testosterone. We reviewed the available literature on metabolic syndrome and hypogonadism with a particular focus on testosterone therapy.
Materials and Methods: A comprehensive MEDLINE review of the world literature from 1988 to 2004 on hypogonadism, testosterone and metabolic syndrome was performed. Results: Observational data suggest that metabolic syndrome is strongly associated with hypogonadism in men. Multiple interventional studies have shown that exogenous testosterone has a favorable impact on body mass, insulin secretion and sensitivity, lipid profile and blood pressure, which are the parameters most often disturbed in metabolic syndrome.
Conclusions: Hypogonadism is likely a fundamental component of metabolic syndrome. Testosterone therapy may not only treat hypogonadism, but may also have tremendous potential to slow or halt the progression from metabolic syndrome to overt diabetes or cardiovascular disease via beneficial effects on insulin regulation, lipid profile and blood pressure. Furthermore, the use of testosterone to treat metabolic syndrome may also lead to the prevention of urological complications commonly associated with these chronic disease states, such as neurogenic bladder and erectile dysfunction. Physicians must be mindful to evaluate hypogonadism in all men diagnosed with metabolic syndrome as well as metabolic syndrome in all men diagnosed with hypogonadism. Future research in the form of randomized clinical trials should focus on further defining the role of testosterone for metabolic syndrome.

J of Clin Endo & Metab. 2005; 90(5): 2618-2623.

Endogenous Sex Hormones and Metabolic Syndrome in Aging Men

M, Grobbee D, et al

Background: Sex hormone levels in men change during aging. These changes may be associated with insulin sensitivity and the metabolic syndrome.
Methods: We studied the association between endogenous sex hormones and characteristics of the metabolic syndrome in 400 independently living men between 40 and 80 yr of age in a cross-sectional study. Serum concentrations of lipids, glucose, insulin, total testosterone (TT), SHBG, estradiol (E2), and dehydroepiandrosterone sulfate (DHEA-S) were measured. Bioavailable testosterone (BT) was calculated using TT and SHBG. Body height, weight, waist-hip circumference, blood pressure, and physical activity were assessed. Smoking and alcohol consumption was estimated from self-report. The metabolic syndrome was defined according to the National Cholesterol Education Program definition, and insulin sensitivity was calculated by use of the quantitative insulin sensitivity check index.
Results: Multiple logistic regression analyses showed an inverse relationship according to 1 SD increase for circulating TT [odds ratio (OR) _ 0.43; 95% confidence interval (CI), 0.32– 0.59], BT (OR _ 0.62; 95% CI, 0.46–0.83), SHBG (OR _ 0.46; 95% CI, 0.33–0.64), and DHEA-S (OR _ 0.76; 95% CI, 0.56–1.02) with the metabolic syndrome. Each SD increase in E2 levels was not significantly associated with the metabolic syndrome (OR _ 1.16; 95% CI, 0.92–1.45). Linear

regression analyses showed that higher TT, BT, and SHBG levels were related to higher insulin sensitivity; _-coefficients (95% CI) were 0.011 (0.008– 0.015), 0.005 (0.001–0.009), and 0.013 (0.010–0.017), respectively, whereas no effects were found for DHEA-S and E2. Estimates were adjusted for age, smoking, alcohol consumption, and physical activity score. Further adjustment for insulin levels and body composition measurements attenuated the estimates, and the associations were similar in the group free of cardiovascular disease and diabetes.
Conclusions: Higher testosterone and SHBG levels in aging males are independently associated with a higher insulin sensitivity and a reduced risk of the metabolic syndrome, independent of insulin levels and body composition measurements, suggesting that these hormones may protect against the development of metabolic syndrome.

Multiple Sclerosis

Arch Neurol. 2007; 64: 683-688.

Testosterone Treatment in Multiple Sclerosis.

Sicotte, N.L., M.D., Giesser, B.S., M.D., et al.

Objective: To study the effect of testosterone supplementation on men with multiple sclerosis (MS).
Design, Setting, and Participants: Men are less susceptible to many autoimmune disease, including MS> possible causes for this include sex hormones and/or sex chromosome effects. Testosterone treatment ameliorates experimental allergic encephalomyelitis, and animal model of MS, but the effect of testosterone supplementation on men with MS is not known. Therefore, 10 men with relapsing-remitting MS were studied using a crossover design whereby each patient served as his own control. There was a 6-month pretreatment period followed by a 12-month period of daily treatment with 10 g of the gel containing 100 mg of testosterone.
Main Outcome Measures: Clinical measures of disability and cognition (the Multiple Sclerosis Functional Composite and the 7/24 Spatial Recall Test) and monthly magnetic resonance imaging measures of enhancing lesion activity and whole brain volumes.
Results: One year of treatment with testosterone gel was associated with improvement in cognitive performance (P=.008) and a slowing of brain atrophy (P<.001). There was no significant effect of testosterone treatment on gadolinium-enhancing lesion numbers (P=.31) or volumes (P=.94). Lean body mass (muscle mass) was increased (P=.02).
Conclusion: These exploratory findings suggest that testosterone treatment is safe and well tolerated and has potential neuroprotective effects in men with relapsing-remitting MS.

Muscle Strength

J Am Geriatr Soc. 2006; 54: 1666–1673.

Androgen Treatment and Muscle Strength in Elderly Men: A Meta-Analysis

Ottenbacher KJ, Ottenbacher ME

OBJECTIVES: To review published, randomized trials examining the effect of androgen treatment on muscle strength in older men.
DESIGN: Systematic review using meta-analysis procedures.
SETTING: Computerized and manual searches.
PARTICIPANTS: MEDLINE, EMBASE, CINAHL, and the Cochrane Register were searched for trials. Key words included testosterone, androgen, sarcopenia, muscle loss, aged, aging, elderly, older; geriatric, randomized controlled trials, and controlled clinical trials. Sixty-five non

overlapping studies were found. Meta-analysis methods were used to evaluate the 11 randomized, double-blind trials.
INTERVENTION: Testosterone or dihydrotestosterone (DHT) replacement therapy in healthy men aged 65 and older.
MEASUREMENTS: Tests of muscle strength.
RESULTS: The studies included 38 statistical comparisons. The mean g-index (gi) adjusted for sample size was 0.53 (95% confidence interval (CI)50.21–0.86). Subanalyses revealed larger effects for measures of lower extremity muscle strength (gi50.63, 95% CI50.03–1.28) than for upper extremity muscle strength (gi50.47, 95% CI50.12–0.84). A larger mean g-index was found for injected (gi50.95, 95% CI50.33–1.58) than topical (gi50.26, 95% CI50.08–0.42) or oral (gi5 _0.21, 95% CI5 _1.40–1.02) administration of testosterone/ DHT. Effect sizes were related to study characteristics such as subject attrition and design-quality ratings. Sensitivity analyses revealed that the elimination of one study reduced the mean g-index from 0.53 to 0.23.
CONCLUSION: The results suggest that testosterone/ DHT therapy produced a moderate increase in muscle strength in men participating in 11 randomized trials. One study influenced the mean effect size.

Prostate

JAMA. 2006; 296: 2351-2361.

Effect of Testosterone Replacement Therapy on Prostate Tissue in Men With Late-Onset Hypogonadism

Marks LS, Mazer NA, et al.

Context: Prostate safety is a primary concern when aging men receive testosterone replacement therapy (TRT), but little information is available regarding the effects of TRT on prostate tissue in men.
Objective: To determine the effects of TRT on prostate tissue of aging men with low serum testosterone levels.
Design, Setting, and Participants: Randomized, double-blind, placebo controlled trial of 44 men, aged 44 to 78 years, with screening serum testosterone levels lower than 300 ng/dL (□10.4 nmol/L) and related symptoms, conducted at a US community-based research center between February 2003 and November 2004.
Intervention: Participants were randomly assigned to receive 150 mg of testosterone enanthate or matching placebo intramuscularly every 2 weeks for 6 months.

Main Outcome Measures: The primary outcome measure was the 6-month change in prostate tissue androgen levels (testosterone and dihydrotestosterone). Secondary outcome measures included 6-month changes in prostate-related clinical features, histology, biomarkers, and epithelial cell gene expression.
Results: Of the 44 men randomized, 40 had prostate biopsies performed both at baseline and at 6 months and qualified for per-protocol analysis (TRT, n=21; placebo, n=19). Testosterone replacement therapy increased serum testosterone levels to the midnormal range (median at baseline, 282 ng/dL [9.8 nmol/L]; median at 6 months, 640 ng/dL [22.2 nmol/L]) with no significant change in serum testosterone levels in matched, placebo-treated men. However, median prostate tissue levels of testosterone (0.91 ng/g) and dihydrotestosterone (6.79 ng/g) did not change significantly in the TRT group. No treatment-related change was observed in prostate histology, tissue biomarkers (androgen receptor, Ki-67, CD34), gene expression (including AR, PSA, PAP2A, VEGF, NXK3, CLU [Clusterin]), or cancer incidence or severity. Treatment-related changes in prostate volume, serum prostate-specific antigen, voiding symptoms, and urinary flow were minor.
Conclusions: These preliminary data suggest that in aging men with late-onset hypogonadism, 6 months of TRT normalizes serum androgen levels but appears to have little effect on prostate tissue androgen levels and cellular functions. Establishment of prostate safety for large populations of older men undergoing longer duration of TRT requires further study.

J Urol. 2003 Dec;170(6 Pt 1):2348-51.

Testosterone replacement therapy in hypogonadal men at high risk for prostate cancer: Results of 1 year of treatment in men with prostatic intraepithelial neoplasia.

Rhoden EL, Morgentaler A.

PURPOSE: One of the greatest concerns among clinicians regarding testosterone replacement therapy (TRT) is the fear of causing or promoting prostate cancer. We evaluated prostatic changes in hypogonadal men with and without high grade prostatic intraepithelial neoplasia (PIN), which is considered a prostatic precancerous lesion, after 1 year of TRT. MATERIALS AND METHODS: A total of 75 hypogonadal who completed 12 months of TRT were studied. All underwent prostate biopsy prior to initiating treatment. Of the men 55 had benign prostate biopsies (PIN-) and 20 had PIN without frank cancer (PIN+). All men with PIN underwent repeat biopsy to exclude cancer prior to the initiation of testosterone treatment. Prostate specific antigen (PSA), and total and free testosterone were determined prior to treatment and at 1 year. Repeat biopsy was performed for a change noted on digital rectal examination or for a PSA increase of 1 ng/l or greater. RESULTS: PSA was similar at baseline in men with and without PIN (1.49 +/- 1.1 and 1.53 +/- 1.6 ng/dl, p >0.05) and after 12 months of TRT (1.82 +/- 1.1 and 1.78 +/- 1.6 ng/dl, respectively, p >0.05). A slight, similar increase in mean PSA was noted in the PIN- and PIN+ groups (0.25 +/- 0.6 and 0.33 +/- 0.6 ng/dl, p >0.05). One man in the PIN+ group had cancer after biopsy was performed due to abnormal digital rectal examination. Four additional men in the PIN- group and 2 in the PIN+ group underwent re-biopsy for elevated PSA and none had cancer. No differences were noted between the PIN- and PIN+ groups with regard to total and free testosterone at baseline and at 1 year (p = 0.267). CONCLUSIONS: After 1 year of TRT men with PIN do not have a greater increase in PSA or a significantly increased risk of cancer than men without PIN. These results indicate that TRT is not contraindicated in men with a history of PIN.

Progesterone

Brain

Ann Emerg Med. 2007; 49: 391-402.

ProTECT: A Randomized Clinical Trial of Progesterone for Acute Traumatic Brain Injury.

Wright, D., et al.

Study objective: Laboratory evidence indicates that progesterone has potent neuroprotective effects. We conducted a pilot clinical trial to assess the safety and potential benefit of administering progesterone to patients with acute traumatic brain injury.
Methods: This phase II, randomized, double-blind, placebo-controlled trial was conducted at an urban Level I trauma center. One hundred adult trauma patients who arrived within 11 hours of injury with a postresuscitation Glasgow Coma Scale score of 4 to 12 were enrolled with proxy consent. Subjects were randomized on a 4:1 basis to receive either intravenous progesterone or placebo. Blinded observers assessed patients daily for the occurrence of adverse events and signs of recovery. Neurologic outcome was assessed 30 days postinjury. The primary safety measures were differences in adverse event rates and 30-day mortality. The primary measure of benefit was the dichotomized Glasgow Outcome Scale–Extended 30 days postinjury.
Results: Seventy-seven patients received progesterone; 23 received placebo. The groups had similar demographic and clinical characteristics. Laboratory and physiologic characteristics were similar at enrollment and throughout treatment. No serious adverse events were attributed to progesterone. Adverse and serious adverse event rates were similar in both groups, except that patients randomized to progesterone had a lower 30-day mortality rate than controls (rate ratio 0.43; 95% confidence interval 0.18 to 0.99). Thirty days postinjury, the majority of severe traumatic brain injury survivors in both groups had relatively poor Glasgow Outcome Scale–Extended and Disability Rating Scale scores. However, moderate traumatic brain injury survivors who received progesterone were more likely to have a moderate to good outcome than those randomized to placebo.
Conclusion: In this small study, progesterone caused no discernible harm and showed possible signs of benefit.

General

Frontiers in Neuroendocrinology. 2006; 27: 340-359.

The many faces of progesterone: A role in adult and developing male brain

Wagner, CK

In addition to its well documented action in female-typical behaviors, progesterone exerts an influence on the brain and behavior of males. This review will discuss the role of progesterone and its receptor in male-typical reproductive behaviors in adulthood and the role of progesterone and its receptor in neural development, in both sexual differentiation of the brain as well as in the development of “nonreproductive” functions. The seemingly inconsistent and contradictory results on progesterone in males that exist in the literature illustrate the complexity of progesterone’s actions and illuminate the need for further research in this area. As progestin-containing contraceptives in men are currently being tested and progesterone administration to pregnant women and premature newborns increases, a better understanding of the role of this hormone in behavior and brain development becomes essential.

Aging Male. 2004; 7(3): 236-257.

Progesterone: the forgotten hormone in men?

Oettel M., Mukhopadhyay A.

'Classical' genomic progesterone receptors appear relatively late in phylogenesis, i.e. it is only in birds and mammals that they are detectable. In the different species, they mediate manifold effects regarding the differentiation of target organ functions, mainly in the reproductive system. Surprisingly, we know little about the physiology, endocrinology, and pharmacology of progesterone and progestins in male gender or men respectively, despite the fact that, as to progesterone secretion and serum progesterone levels, there are no great quantitative differences between men and women (at least outside the luteal phase). In a prospective cohort study of 1026 men with and without cardiovascular disease, we were not able to demonstrate any age-dependent change in serum progesterone concentrations. Progesterone influences spermiogenesis, sperm capacitation/acrosome reaction and testosterone biosynthesis in the Leydig cells. Other progesterone effects in men include those on the central nervous system (CNS) (mainly mediated by 5α-reductase progesterone metabolites as so-called neurosteroids), including blocking of gonadotropin secretion, sleep improvement, and effects on tumors in the CNS (meningioma, fibroma) as well as effects on the immune system, cardiovascular system, kidney function, adipose tissue, behavior, and respiratory system. A progestin may stimulate weight gain and appetite in men as well as women. The detection of progesterone receptor isoforms would have a highly diagnostic value in prostate pathology (benign prostatic hypertrophy and prostate cancer). The modulation of progesterone effects on typical male targets is connected with a great pharmacodynamic variability. The reason for this is that, in men, some important effects of progesterone are mediated non-genomically through different molecular biological modes of action. Therefore, the precise therapeutic manipulation of progesterone actions in the male requires completely new endocrine-pharmacological approaches.

DHEA

General

Alternative Medicine Review. 1996; 1 (2): 60-69.

Dehydroepiandrosterone: Biological Effects and Clinical Significance

Gaby A

Dehydroepiandrosterone (DHEA) is a steroid hormone secreted in greater quantity by the adrenal glands than any other adrenal steroid. For many years, scientists assumed that DHEA merely functioned as a reservoir upon which the body could draw to produce other hormones, such as estrogen and testosterone. However, the recent identification of DHEA receptors in the liver, kidney and testes of rats strongly suggests that DHEA may have specific physiologic actions of its own. Circulating levels of DHEA decline progressively with age; this age-related decline does not occur with any of the other adrenal steroids. Epidemiologic evidence indicates that higher DHEA levels are associated with increased longevity and prevention of heart disease and cancer, suggesting that some of the manifestations of aging may be caused by DHEA deficiency. Animal and laboratory data indicate that administration of DHEA may prevent obesity, diabetes, cancer (breast, colon and liver), and heart disease; enhance the functioning of the immune system; and prolong life. In humans, evidence exists that DHEA might be associated with autoimmune diseases such as lupus, rheumatoid arthritis and multiple sclerosis; chronic fatigue syndrome; acquired immunodeficiency syndrome (AIDS); allergic disorders; osteoporosis; and Alzheimer's disease. Although administration of DHEA appears to be safe, its long-term effects are unknown, and it is possible that adverse consequences will become evident with chronic use. It is therefore important that this hormone be used with care and that practitioners err on the side of caution when contemplating DHEA supplementation.

Arch Gen Psychiatry. 2005; 62: 154-162.

Dehydroepiandrosterone Monotherapy in Midlife-Onset Major and Minor Depression

Schmidt P, Daly R

Context: Alternative and over-the-counter medicines have become increasingly popular choices for many patients who prefer not to take traditional antidepressants. The adrenal androgen and neurosteroid dehydroepiandrosterone (DHEA) is available as over-the counter hormonal therapy and previously has been reported to have antidepressant-like effects.
Objective: To evaluate the efficacy of DHEA as a monotherapy treatment for midlife-onset depression.
Design: A double-blind, randomized, placebo controlled, crossover treatment study was performed from January 4, 1996, through August 31, 2002.
Settings: The National Institute of Mental Health Midlife Outpatient Clinic in the National Institutes of Health Clinical Center, Bethesda, Md.
Patients: Men (n=23) and women (n=23) aged 45 to 65 years with midlife-onset major or minor depression participated in this study. None of the subjects received concurrent antidepressant medications.
Intervention: Six weeks of DHEA therapy, 90 mg/d for 3 weeks and 450 mg/d for 3 weeks, and 6 weeks of placebo.

Main Outcome Measures: The 17-Item Hamilton Depression Rating Scale and Center for Epidemiologic Studies Depression Scale. Additional measures included the Derogatis Interview for Sexual Functioning. Results were analyzed by means of repeated-measures analysis of variance and post hoc Bonferroni t tests.
Results: Six weeks of DHEA administration was associated with a significant improvement in the 17-Item Hamilton Depression Rating Scale and the Center for Epidemiologic Studies Depression Scale ratings compared with both baseline (P_.01) and 6 weeks of placebo treatment (P_.01). A 50% or greater reduction in baseline Hamilton Depression Rating Scale scores was observed in 23 subjects after DHEA and in 13 subjects after placebo treatments. Six weeks of DHEA treatment also was associated with significant improvements in Derogatis Interview for Sexual Functioning scores relative to baseline and placebo conditions.
Conclusion: We find DHEA to be an effective treatment for midlife-onset major and minor depression.

Bone

J Clin Endocrinol Metab. 2006; 91: 2986–2993.

Effects of Dehydroepiandrosterone Replacement Therapy on Bone Mineral Density in Older Adults: A Randomized, Controlled Trial

Jankowski CM, Gozansky WS,

Context: Dehydroepiandrosterone (DHEA) and its sulfate (DHEAS) decrease with aging and are important androgen and estrogen precursors in older adults. Declines in DHEAS with aging may contribute to physiological changes that are sex hormone dependent.
Objective: The aim was to determine whether DHEA replacement increases bone mineral density (BMD) and fat-free mass.
Design, Setting, and Participants: A randomized, double-blinded, controlled trial was conducted at an academic research institution. Participants were 70 women and 70 men, aged 60–88 yr, with low serum DHEAS levels.
Intervention: The intervention was oral DHEA 50 mg/d or placebo for 12 months.
Measurements: BMD, fat mass, and fat-free mass were measured before and after intervention.
Results: Intent-to-treat analyses revealed trends for DHEA to increase BMD more than placebo at the total hip (1.0%, P _ 0.05), trochanter (1.2%, P_0.06), and shaft (1.2%, P_0.05). In women only, DHEA increased lumbar spine BMD (2.2%, P _ 0.04; sex-by-treatment interaction, P _ 0.05). In secondary compliance analyses, BMD increases in hip regions were significant (1.2–1.6%; all P _ 0.02) in the DHEA group. There were no significant effects of DHEA on fat or fat-free mass in intent-to-treat or compliance analyses.
Conclusions: DHEA replacement therapy for 1 yr improved hip BMD in older adults and spine BMD in older women. Because there have been few randomized, controlled trials of the effects of DHEA therapy, these findings support the need for further investigations of the benefits and risks of DHEA replacement and the mechanisms for its actions.

Hydrocortisone

Chronic Fatigue Syndrome

Lancet. 1999; 353: 455-58.

Low-dose hydrocortisone in chronic fatigue syndrome: a randomized crossover trial

Cleare AJ, Heap E, et al.

Background: Reports of mild hypocortisolism in chronic fatigue syndrome led us to postulate that low-dose hydrocortisone therapy may be an effective treatment.
Methods: In a randomised crossover trial, we screened 218 patients with chronic fatigue syndrome without co-morbid psychiatric disorder. The eligible patients received consecutive treatment with low-dose hydrocortisone (5mg or 10mg daily) for 1 month and placebo for 1 month; the order of treatment was randomly assigned. Analysis was by intention to treat.
Findings: None of the patients dropped out. Compared with the baseline self-reported fatigue scores (mean 25.1 points), the score fell by 7.2 points for patients on hydrocortisone and by 3.3 points for those on placebo (paired difference in mean scores 4.5 points [85% CI 1.2-7.7], p=0.009. in nine (28%) of the 32 patients on hydrocortisone, fatigue scores reached a predefined cut-off value similar to the normal population score, compared with three (9%) of the 32 on placebo (Fisher's exact test p=0.05). the degree of disability was reduced with hydrocortisone treatment, but not with placebo. Insulin stress tests showed that endogenous adrenal function was not suppressed by hydrocortisone. Minor side effects were reported by three patients after hydrocortisone treatment and by one patient after placebo.
Interpretation: In some patients with chronic fatigue syndrome, low-dose hydrocortisone reduces fatigue levels in the short term. Treatment for a longer time and follow-up studies are needed to find out whether this effect could be clinically useful.

J Clin Endocrinol Metab. 2001; 86: 3545-3554.

Hypothalamo-Pituitary-Adrenal Axis Dysfunction in Chronic Fatigue Syndrome, and the Effects of Low-Dose Hydrocortisone Therapy

Cleare AJ, Miell J, Heap E, et al.

These neuroendrocrine studies were part of a series of studies testing the hypothesis that 1) there may be reduced activity of the hypothalamic-pituitary-adrenal axis in chronic fatigue syndrome and 2) low-dose augmentation with hydrocortisone therapy would improve the core symptoms. We measured ACTH and cortisol responses to human CRH, the insulin stress test, and D-fenfluramine in 37 medication-free patients with CDC-defined chronic fatigue syndrome but no comorbid psychiatric disorders and 28 healthy controls. We also measured 24-hour urinary free cortisol in both groups. All patients (n=37) had a pituitary challenge test (human CRH) and a hypothalamic challenge test [either the insulin stress test (n=16) or D-fenfluramine (n=21)]. Baseline cortisol concentrations were significantly raised in the chronic fatigue syndrome group for the human CRH test only. Baseline ACTH concentrations did not differ between groups for any test. ACTH responses to human CRH, the insulin stress test, and D-fenfluramine were similar for patient and control groups. Cortisol responses to the insulin stress test did not differ between groups, but there was a trend for cortisol responses both to human CRH and D-fenfluramine to be lower in the chronic fatigue syndrome group. These differences were significant when ACTH

responses were controlled. Urinary free cortisol levels were lower in the chronic fatigue syndrome group compared with the healthy group. These results indicate that ACTH responses to pituitary and hypothalamic challenges are intact in chronic fatigue syndrome and do not support previous findings of reduced central responses in hypothalamic-pituitary-adrenal axis function or the hypothesis of abnormal CRH secretion in chronic fatigue syndrome. These data further suggest that hypocortisolism found in chronic fatigue syndrome may be secondary to reduced adrenal gland output. Thirty-two patients were treated with a low-dose hydrocortisone regime in a double-blind, placebo-controlled crossover design, with 28 days on each treatment. They underwent repeated 24-h urinary cortisol collections, a human CRH test, and a insulin stress test after both active and placebo arms of treatment. Looking at all subjects, 24-h urinary free cortisol was higher after active compared with placebo treatments, but 0900-h cortisol levels and the ACTH and cortisol responses to human CRH and insulin stress test did not differ. However, a differential effect was seen in those patients who responded to active treatment (defined as a reduction in fatigue score to the median population level or less). In this group, there was a significant increase in the cortisol response to human CRH, which reversed the previously observed blunted responses seen in these patients. We conclude that the 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.

Psychoneuroendocrinology. 2004 Jul; 29(6): 724-32.

Levels of DHEA and DHEAS and responses to CRH stimulation and hydrocortisone treatment in chronic fatigue syndrome.

Cleare AJ, O'Keane V, Miell JP

Background: An association between chronic fatigue syndrome (CFS) and abnormalities of the hypothalamo-pituitary-adrenal axis has been described, and other adrenal steroid abnormalities have been suggested. Dehydroepiandrostenedione (DHEA) and its sulphate (DHEA-S), apart from being a precursor of sex steroids, have other functions associated with memory, depression and sleep. It has been suggested that CFS may be associated with a state of relative DHEA(-S) deficiency. Therefore we investigated basal levels of DHEA(-S), the cortisol/DHEA molar ratio and the responsiveness of DHEA to stimulation by corticotrophin-releasing hormone (CRH). Recent studies have also suggested that low dose hydrocortisone may be effective at reducing fatigue in CFS. We therefore also assessed these parameters prior to and following treatment with low dose oral hydrocortisone.
Methods: Basal levels of serum DHEA, DHEAS and cortisol were measured in 16 patients with CFS without depression and in 16 controls matched for age, gender, weight, body mass index and menstrual history. CRH tests (1 g/kg i.v.) were carried out on all subjects and DHEA measured at 0, +30 and +90 min. In the patient group, CRH tests were repeated on two further occasions following treatment with hydrocortisone (5 or 10 mg, p.o.) or placebo for 1 month each in a double-blind cross over study protocol.
Results: Basal levels of DHEA were higher in the patient, compared to the control, group (14.1+/-2.2 vs. 9.0+/-0.90 ng/ml, P=0.04), while levels of DHEAS in patients (288.7+/-35.4 microg/dl) were not different from controls (293.7+/-53.8, P=NS). Higher DHEA levels were correlated with higher disability scores. Basal cortisol levels were higher in patients, and consequently the cortisol/DHEA molar ratio did not differ between patients and controls. Levels of DHEA (8.9+/-0.97 ng/ml, P=0.015) and DHEAS (233.4+/-41.6 microg/dl, P=0.03) were lower in patients following treatment with hydrocortisone. There was a rise in DHEA responsiveness to CRH in the patients after treatment but this did not attain significance (AUCc: 2.5+/-1.7 ng/ml h pre-treatment vs. 6.4+/-1.2 ng/ml h post-hydrocortisone, P=0.053). However, those patients who responded fully to hydrocortisone in terms of reduced fatigue scores did show a significantly increased DHEA responsiveness to CRH (AUCc: -1.4+/-2.5 ng/ml h at baseline, 5.0+/-1.2 ng/ml h after active

treatment, P=0.029). Conclusions: DHEA levels are raised in CFS and correlate with the degree of self-reported disability.

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