References: Healthy aging medicine

Anti-aging medicine is a movement of practitioners

Hormone therapies in anti-aging medicine

Premier article sur l’evidence-based medicine

Recommendations to make growth hormone illegal for anti-aging purposes

Preventing the making of growth hormone illegal
14. IHS letter to the US senate commission on GH available on www.wosaam.ws

Preconceived idea that aging is not or poorly evitable and reversible

Aging is not inevitable, nor irreversible

Preconceived idea that overreliance on blood tests alone to diagnose a hormone deficit or excess, excluding anamnesis, physical exam, other type of laboratory tests

The predominance of blood tests and its reference values
21. Surks MI, Goswami G, Daniels GH. The thyrotropin reference range should remain unchanged. J Clin Endocrinol Metab. 2005 Sep;90(9):5489-96. Review

The need for optimal TSH ranges to interpret the serum TSH test
22. Dickey RA, Wartofsky L, Feld S. Optimal thyrotropin level: normal ranges and reference intervals are not equivalent. Thyroid. 2005 Sep;15(9):1035-9. Review. (support of a narrower, optimal or true normal range for thyrotropin (TSH) of 0.4 to 2.5 mIU/L, based on clinical results and recent information on the relatively stable and narrow range of values in patients without thyroid disease)
Thyroid treatment trials (therapeutic test): improved hypothyroid symptoms in patients with thyroid treats within the reference range, confirming the diagnosis of (initial) underactive thyroid function

Depression: Beneficial thyroid treatment of “euthyroid” depressive patients, preferably with T3 (triiodothyronine)
24. Atshuler LL, Bauer M, Frye MA, Gitlin MJ, Mintz J, Szuba MP, Leight KL, Whybrow PC. Does thyroid supplementation accelerate tricyclic antidepressant response? A review and meta-analysis of the literature. Am J Psychiatry. 2001 Oct;158(10):1617-22 (six double-blind, placebo-controlled studies assessing the concomitant administration of thyroid hormone and antidepressant to accelerate clinical response in patients with nonrefractory depression. Five of the six studies found T(3) to be significantly more effective than placebo in accelerating clinical response. The pooled, weighted effect size index was 0.58, and the average effect was highly significant. Further, the effects of T(3) acceleration were greater as the percentage of women participating in the study increased.)
27. Abraham G, Milev R, Stuart Lawson J. T3 augmentation of SSRI resistant depression. J Affect Disord. 2006 Apr;91(2-3):211-5. (open study thyroid-stimulating hormone (TSH) value within the normal range.. T3 augmentation resulted in improvement of mood scores. The responders’ rate of 42% in our study is comparable to the response rates reported using T3 or lithium to augment tricyclic antidepressants or other combination strategies used to treat resistant depression
31. Sokolov ST, Levitt AJ, Joffe RT. Thyroid hormone levels before unsuccessful antidepressant therapy are associated with later response to T3 augmentation. Psychiatry Res. 1997 Mar 24;69(2-3):203-6.
35. Cooke RG, Joffe RT, Levitt AJ. T3 augmentation of antidepressant treatment in T4-replaced thyroid patients. J Clin Psychiatry. 1992 Jan;53(1):16-8. (T3 augmentation therapy for eight depressed patients who had not responded to an adequate antidepressant drug trial and who were receiving T4 therapy for thyroid disease. T3 was prescribed in open-label fashion, and response was judged by the clinician, whose assessment was supplemented by the use of standardized rating scales. Seven of the nine patients were judged to respond to T3 augmentation.)

Hypercholesterolemia: significant reduction with thyroid treatment in “euthyroid” hypercholesterolemic patients with auto-immune thyroid disease
Euthyroid goiter is usually treated with TSH-inhibitory doses of levo-T(4) (L-T(4))


Pregnancy in euthyroid women with autoimmune thyroiditis: Thyroxin therapy is able to lower the chance of miscarriage and premature delivery.


Thyroxine treatment trials to biochemically “euthyroid” patients with treated (drug-normalized) Graves’ disease that reduced the levels of thyroid antibodies


Thyroxine treatment trials to biochemically “euthyroid” patients with Hashimoto’s thyroiditis that reduced the levels of thyroid antibodies


55. Padberg S, Keller K, Usadel KH, Schunn-Dreager PM. One-year prophylactic treatment of euthyroid Hashimoto's thyroiditis patients with levothyroxine: is there a benefit? Thyroid. 2001 Mar;11(3):249-55. Medica Clinic I, Endocrinology, Center of Internal Medicine, Johann Wolfgang Goethe-University, Frankfurt/Main, Germany


A thyroxine treatment trial (therapeutic test) that did not significantly improve hypothyroid symptoms in patients with thyroid tests within the reference range

A thyroxine treatment trial to biochemically “euthyroid” patients with Hashimoto’s thyroiditis that did not significantly reduce the levels of anti-thyroid peroxidase antibodies


Disputes on the validity of using the blood tests and its laboratory reference ranges for the diagnosis of hypothyroidism


61. Shepherd C. Giving thyroid hormones to clinically hypothyroid but biochemically euthyroid patients. Long-term treatment is being used. BMJ. 1997 Sep 27;315(7111):814.


63. http://www.brodabarnes.org

64. http://thyroid.about.com/bio/Mary-Shomon-350.htm

Preconceived idea that thyroxine alone as treatment of hypothyroidism

Dogma on the use of thyroxine alone to treat hypothyroidism


Disputes on the T4 alone treatment dogma and arguments for thyroid preparations associating T3 and T4


Double-blind randomized controlled trials with significant superior effects of T4-T3 versus T4 alone


Double-blind randomized controlled study with near significantly superior effects of T4-T3 versus T4 alone

72. Bunevicius R, Jakubonien N, Jurkevicius R, Cernicat J, Lasas L, Prange AJ. Thyroxine vs thyroxine plus triiodothyronine in treatment of hypothyroidism after thyroidectomy for Graves’ disease. Endocrine. 2002 Jul;18(2):129-33 Institute of Endocrinology, Clinic of the Kaunas Medical University, Lithuania. (no significant differences were found on measures of mood, cognition, or physiologic variables between treatments, but symptoms of hypothyroidism and of hyperthyroidism tended to decrease on a standard symptom scale after combined treatment, mental state tended to improve on some mood scales)

Double-blind randomized controlled trials with no superior significant effects of T4-T3 versus T4 alone, but more patients preferring T4/T3 than T4 alone


74. Saravanan P, Simmons DJ, Greenwood R, Peters TJ, Dayan CM. Partial substitution of thyroxine (T4) with triiodothyronine in patients on T4 replacement therapy: results of a large community-based randomized controlled trial. J Clin Endocrinol Metab. 2005 Feb;90(2):805-12. University of Bristol, Whitson Street, Bristol BS1 3NY, UK. (697 hypothyroid patients, a subgroup of patients showing transient improvement after partial substitution with T(3))
Double-blind randomized controlled trial with no superior significant effects of T4-T3 versus T4 alone, but patients with T3-T4 kept a higher TSH (indicative of a too low dose)


Double-blind randomized controlled trial with globally no superior significant effects of T4-T3 versus T4 alone, except on one parameter where the patients onT4-T3 combinations did better:


Double-blind randomized controlled trials with no superior effects of T4-T3 versus T4 alone


Non-randomized controlled trials with no superior significant effects of T4-T3 versus T4 alone, but more patients preferring T4/T3 than T4 alone


Open study where switching patients from thyroxine to T3/4 combinations improved their symptoms


Other studies suggesting that T3-T4 (and T3) treatments work better than T4

82. Kloppenburg M, Dijkmans BA, Rasker JJ. Effect of therapy for thyroid dysfunction on musculoskeletal symptoms. Clin Rheumatol. 1993 Sep;12(3):341-5 (since thyroxin is used much less improvement of theumatoi'd disorders that previously when T3 or T3/T4 preparations were used)


In humans, T4-T3 treatments reduce serum cholesterol and increase the speed of the Achilles tendon reflexes better than T4 treatments alone


When T3 and T4 are both supplemented to the food simultaneously with goitrogens, a much better prevention of goiter is obtained than when solely T4 is added, even if T4 is given at doses 7 times higher those of T3-T4 treatments

A study in rats rendered hypothyroid shows that cellular euthyroidism is only obtained in the target organs of hypothyroid rats if T3 is added to the classic T4 medication


Medications with T4 alone do not succeed in achieving complete cellular euthyroidism in the target organs, probably because T3 is really the active hormone


T3 is much more potent than T4


Preconceived idea that testosterone therapy avoidance in men based on the belief that testosterone causes prostate cancer

Arguments against the use of testosterone therapies:

Studies that suggest that testosterone may increase the prostate cancer risk

Prostate cancer: the association with high free testosterone levels

94. Pierorazio PM, Ferrucci L, Kettermann A, Longo DL, Metter EJ, Carter HB. Serum testosterone is associated with aggressive prostate cancer in older men: results from the Baltimore Longitudinal Study of Aging. BJU Int. 2009 Sep 14. [Epub ahead of print] (the researchers found a positive association between the free testosterone index in the serum with aggressive high-risk prostate cancer - death from prostate cancer - for men above age 65, not in younger men)

95. Yano M, Imamoto T, Suzuki H, Fukasawa S, Kojima S, Komiya A, Naya Y, Ichikawa T. The clinical potential of pretreatment serum testosterone level to improve the efficiency of prostate cancer screening. Eur Urol. 2007 Feb;51(2):375-80. (ambivalent study that compares prostate cancer patients with a wrong control group, namely patients with benign prostate hypertrophy (who tend to have an increased conversion of testosterone to estradiol, cause of their stromal hyperplasia) and not to healthy controls with smaller prostates without prostate disease. See Kwon T, et l. BJU Int. 2010 Jan 8. study that shows prostate cancer more easily appears in men with smaller prostate volume, the opposite of benign prostate hypertrophy. In this study, initially higher serum testosterone predict a higher risk of prostate cancer at biopsy, but when prostate cancer is found, higher serum testosterone are associated with less aggressive disease)

96. Parsons JK, Carter HB, Platz EA, Wright EJ, Landis P, Metter EJ. Serum testosterone and the risk of prostate cancer: potential implications for testosterone therapy. Cancer Epidemiol Biomarkers Prev. 2005 Sep;14(9):2257-60 (critics: a potential bias may come from nutritional factors: individuals who eat a lot of food related to a higher cancer risk such as meat, particularly if cooked well-done, and/or milk, have also higher levels of testosterone as well as of other hormones associated with a higher cancer risk. Moreover, there is no information in this study on estradiol levels. This is important as the simultaneous presence of high levels of testosterone and estradiol may, following certain reports, increase the prostate cancer (PC) risk, not testosterone levels alone; heavy alcohol drinking, another risk factor for PC, that is in some countries of the world frequent can considerably increase both the estradiol levels and the PC risk in consumers. Other possible bias: data were not adjusted for other PC risk factors such as smoking, nutritional deficiencies, etc.)

97. Mydlo JH, Tieng NL, Volpe MA, Chaiken R, Kral JG. A pilot study analyzing PSA, serum testosterone, lipid profile, body mass index and race in a small sample of patients with and without carcinoma of the prostate. Prostate Cancer Prostatic Dis. 2001;4(2):101-105 (critics: no dietary factors were taken into account, only high BMI as a risk factor, nore was serum SHBG analysed: dehydrated persons have usually high SHBG, and thus higher total testosterone, which is bound to it, but generally low active, bioavalable and free testosterone levels)


A study where higher levels of testosterone were found in patients who are in the advanced D-stage of PC, compared to the levels found in patients in the more moderate B and C-stages of prostate cancer

100. Imamoto T, Suzuki H, Akakura K, Komiya A, Nakamachi H, Ichikawa T, Igarashi T, Ito H. Pretreatment serum level of testosterone as a prognostic factor in Japanese men with hormonally treated stage D2 prostate cancer. Endocr J. 2001 Oct;48(5):573-8 (note: but those in D-stage that had the highest testosterone had the best prognosis, including longer cancer-free survival time)

A study where a higher rate of metastasis (-relapse) is found in prostate cancer patients with testosterone > 500 ng/dl that have been locally irradiated (critic: the irradiation may change the risk)


A study where testosterone treatment of one patient would have caused prostate cancer ( Huggins started the belief that prostate cancer could be caused by testosterone in 1941)


A study where testosterone treatment increases the growth of prostate cancer: in vitro


Arguments for the use of testosterone therapies

Human studies:

Recent review and meta-analysis studies that state that

- Serum androgen levels, within a broad range, are not associated with prostate cancer risk.
- at time of prostate cancer diagnosis, low rather than high serum testosterone levels have been found to be associated with advanced or high-grade disease.
- The available evidence indicates that testosterone therapy neither increases the risk of prostate cancer diagnosis nor affects the progression of prostate cancer, nor the prostate cancer recurrence in men who have undergone definitive treatment without residual disease;


105. Michaud JE, Billups KL, Partin AW. Testosterone and prostate cancer: an evidence-based review of pathogenesis and oncologic risk. Ther Adv Urol. 2015 Dec;7(6):379-87. (While data from large, prospective, randomized, controlled trials are absent, TRT in select prostate cancer patients is likely safe. In the end)


107. Kühn CM, Strasser H, Romming A, Wulich B, Goebell PJ. Testosterone Replacement Therapy in Hypogonadal Men Following Prostate Cancer Treatment: A Questionnaire-Based Retrospective Study among Urologists in Bavaria, Germany. Urol Int. 2015;95(2):153-9. (there is no clear evidence to withhold TRT from hypogonadal men after curative PCa treatment.)


Low serum testosterone levels have been found in prostate cancer patients


Close to statistical significance lower testosterone levels in prostate cancer patients

Low testosterone levels are found in prostate cancer patients and in their (not yet affected) relatives with familial predisposition to prostate cancer

A high serum SHBG (and thus less bioavailable testosterone) is found in men with family history of prostate cancer

A high incidence of prostate cancer is found in patients with low testosterone and normal digital rectal examination and normal PSA (≤ 4 ng/ml)

Low serum levels of total and bioavailable testosterone are found in populations with a higher risk of prostate cancer (such as African-Americans and whites)

Studies where a low serum dihydrotestosterone (DHT) was found in prostate cancer patients
A study where DHT is inversely, significantly, and strongly associated with the risk of prostate cancer

A low serum level of androstanediol glucuronide, the major androgen metabolite, increases the risk of prostate cancer.

High grade prostate cancers are associated with low testosterone levels, suggesting that higher testosterone levels may protect against progression of prostate cancer to more aggressive forms (higher Gleason score &/or locally invasive &/or metastatic)

Lack of preoperative low serum testosterone is associated with high-grade prostate cancer and an increased Gleason score upgrading.

Presence of prostate cancer affects serum testosterone levels in clinically localized prostate cancer patients.


Lack of preoperative low serum testosterone is associated with high-grade prostate cancer and an increased Gleason score upgrading.


Kwon T, Jeong IG, You D, Park MC, Hong JH, Ahn H, Kim GS. Effect of prostate size on pathological outcome and biochemical recurrence after radical prostatectomy for prostate cancer: is it correlated with serum testosterone level? BJU Int. 2010 Jan 8. [Epub ahead of print] (low serum testosterone is associated with greater prostate malignancy, but not with an increased risk of prostate cancer recurrence)


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Kwon T, Jeong IG, You D, Park MC, Hong JH, Ahn H, Kim GS. Effect of prostate size on pathological outcome and biochemical recurrence after radical prostatectomy for prostate cancer: is it correlated with serum testosterone level? BJU Int. 2010 Jan 8. [Epub ahead of print] (low serum testosterone is associated with greater prostate malignancy, but not with an increased risk of prostate cancer recurrence)


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Lack of preoperative low serum testosterone is associated with high-grade prostate cancer and an increased Gleason score upgrading.

Gene polymorphisms with increased risk of high grade prostate cancer are associated with low testosterone levels


Metastatic prostate cancer (PC) is associated with a low serum testosterone compared to localized PC


A study that shows that the response to prostate cancer therapy is better in prostate cancer patients with higher serum testosterone, while a low serum testosterone level in these patients predicts a worse response to androgen withdrawal therapy (progression to androgen-independent prostate cancer)


Much lower prostate level of dihydrotestosterone in the prostate tissue of prostate cancer patients than in noncancerous patients


Lower prostate tissue levels of DHT (but similar levels of testosterone) are found in men with recurrent prostate cancer compared to men with benign prostate hypertrophy


Low testosterone levels are associated with increased prostate cancer mortality in prostate cancer patients


Low testosterone levels are associated with increased overall mortality in prostate cancer patients

Studies that show that prostate cancer patients who recover normal testosterone levels after androgen deprivation therapy have less morbidity, less biochemical progression and/or a better survival rate than PC men whose testosterone remain low after therapy (by remaining on androgen deprivation or no recovering their testosterone levels after stop of androgen deprivation)


A study where low testosterone levels are found in men with benign prostate hypertrophy


A study where a low androstanediol glucuronide level was found in patients with benign prostate hypertrophy


Men with chronic prostatitis have often low testosterone

185. Yunda IF, Imshinetskaya LP. Testosterone excretion in chronic prostatitis. Andrologia. 1977 Jan-Mar:9(1):89-94 (In 73.1% of patients considerable reduction of testosterone excretion was revealed. Reduction of testicular endocrine function is in direct correllative dependence on severity of clinical symptoms, duration of disease and form of chronic prostatitis.)

A history of prostatitis is positively associated with a history of benign prostatic hyperplasia and cancer

186. Daniels NA, Ewing SK, Zmuda JM, Wilt TJ, Bauer DC; Osteoporotic Fractures in Men (MrOS) Research Group. Correlates and prevalence of prostatitis in a large community-based cohort of older men. Urology. 2005 Nov;66(5):964-70 ("We found positive associations for a history of prostatitis with a history of benign prostatic hyperplasia (odds ratio 8.0, 95% confidence interval 6.8 to 9.5) and a history of prostate cancer (odds ratio 5.4, 95% CI: 4.4 to 6.6")

A study where testosterone treatment at high doses prevented the prostate stromal proliferation that estradiol may induce in the presence of physiological concentrations of testosterone


Studies where testosterone treatment appears to protect against prostate cancer


Studies where testosterone/androgen treatment of patients with advanced prostate cancer increased their survival time and quality of life


Studies where testosterone/androgen treatment inhibits the proliferation of human prostate cancer cells or induces their apoptosis in vitro


Studies where testosterone treatment reduces prostate dysfunction complaints (dysuria, nocturia)


197. Kears W. M. Testosterone in the treatment of testicular deficiency and prostatic enlargement. Wisconsin Med J. 1941; 40:927 (testosterone propionate therapy did not reduce the size of the prostate, but reduced the dysuria)

198. Meltzer M. Male hormone therapy of prostatic hypertrophy. Lancet. 1939; 59: 279


201. Markham MJ. The clinical use of testosterone propionate in benign prostatic hypertrophy. Urol Cutan Rev. 1941; 45:35


Studies where dihydrotestosterone treatment reduced the prostate volume (-15 to -20% after 1 year treatment)


Animal studies:

A study that shows that androgen deprivation (castration) stimulates the progression of androgen-independent prostate cancer in mice in vivo


A study that shows that androgen deprivation stimulates the progression of hormone-sensitive mouse prostate cancer cells to hormone insensitive in vitro


Studies where antiandrogens (which cause androgen deficiency) may promote DMAB-induced prostate cancer incidence or increase its malignancy


A study where significantly lower testosterone (and androstenedione) levels are found in mice with prostate inflammation. This means that testosterone (and androstenedione) may be necessary to counter prostate inflammation


A study where testosterone treatment may prevent benign prostate hypertrophy by inhibiting stromal proliferation-induced by estradiol and by keeping prostate glandular cells health, preventing their atrophy in vitro
A study where testosterone treatment reduces the proliferation of mouse prostate cancer cells in vitro


A study where testosterone treatment reduces the proliferation of guinea pig prostate stroma cells in vitro


A study where testosterone treatment at high doses does not increase the incidence of prostate cancer cells in mice

Mainwaring WI. The effect of testosterone on the age-associated changes in the ventral prostate gland of the mouse. Testosterone and ageing of the prostate. Gerontologia. 1968;14(1):133-41

A study where testosterone, DHT and progesterone protects the prostate glandular epithelium against metaplasia and excessive stroma proliferation induced by estrogens in castrated male mice


Mechanisms of testosterone’s or DHT’s presumed protective action against prostate cancer development

Studies that show that testosterone can stimulate the production of reactive oxygen species in prostate cancer cells, reducing their growth rate and making their survival more difficult

Sun XY, Donald SP, Phang JM. Testosterone and prostate specific antigen stimulate generation of reactive oxygen species in prostate cancer cells. Carcinogenesis. 2001 Nov;22(11):1775-80


A study where dihydrotestosterone treatment stimulates apoptosis of prostate cancer cells


Neutral effects of testosterone therapies

Review studies where the authors did not find an adverse effect of testosterone levels or treatment on the prostate cancer risk
Review studies with conclusions that there is no data to support the view that testosterone treatment could increase the risk of prostate cancer, making e.g. a prostate cancer progress from a preclinical to a clinical stage

224. Rhoden NE. NEJM 2004 ("No compelling evidence at present to suggest that men with higher testosterone levels are at greater risk of prostate cancer or that treating men who have hypogonadism with exogenous androgens increases this risk. In fact, it should be recognized that prostate cancer becomes more prevalent exactly at the time of a man's life when testosterone levels decline.")

225. Morales A. Androgen replacement therapy and prostate safety. Eur Urol 2002 Feb;41(2):113-20 ("To date there is no evidence that exogenous androgens promote development of prostate cancer")

226. Basaria S, Wahlstrom JT, Dobs AS. Anabolic-Androgenic Steroid Therapy in the Treatment of Chronic Diseases. J Clin Endocrinol Metab. 2001 Nov;86(11):5108-17 ("recent reviews suggest that the incidence of prostate cancer is not increased by testosterone administration")

227. Morley JE. Testosterone replacement and the physiologic aspects of aging in men. Mayo Clin Proc. 2000 Jan;75 Suppl:S83-7 ("There is no clinical evidence that the risk of either prostate cancer or benign prostate hypertrophy increases with testosterone treatment")


230. Prehn RT. On the prevention and therapy of prostate cancer by androgen administration. Cancer Res. 1999 Sep;59(17):4161-4 ("... contrary to prevalent opinion, declining rather than high levels of androgens probably contribute more to human prostate carcinogenesis and ... androgen supplementation would probably lower the incidence of the disease. ... consider the possibility that the growth of androgen-independent prostate cancers might be reduced by the administration of androgens")

Studies that show that the incidence of prostate cancer is not higher in men treated with testosterone than in the general population of the same age, despite the fact that men on testosterone treatment undergo more prostate checks and thus have greater chances of having a prostate cancer detected ("the cancer rate in testosterone replacement treatment trials is only approximately 1%, similar to detection rates in screening programs")

231. Coward RM, Simhan J, Carson CC. 3rd. Prostate-specific antigen changes and prostate cancer in hypogonadal men treated with testosterone replacement therapy. BJU Int. 2005 May;103(9):1179-83 (the incidence of prostate cancer among men with late-onset hypogonadism on testosterone replacement therapy is no greater than that in the general population)

232. Dobs AS, Morgentaler A. Does testosterone therapy increase the risk of prostate cancer? Endocr Pract. 2008 Oct;14(7):904-11 ("reviewed studies investigating the relationship between testosterone therapy and prostate cancer progression. ... No evidence of an associated relationship between exogenous testosterone therapy and prostate cancer has emerged from clinical trials or adverse event reports")

233. Morgentaler A, Trash AM. Shifting the paradigm of testosterone and prostate cancer: the saturation model and the limits of androgen-dependent growth. Eur Urol. 2009 Feb;55(2):310-20 ("A literature search was performed of publications dating from 1941 to 2008 that addressed experimental and clinical effects of androgens on prostate growth ... maximal androgen-receptor binding is achieved at serum testosterone concentrations well below the physiologic range.... The evidence clearly indicates that there is a limit to the ability of androgens to stimulate prostate cancer growth")

234. Morgentaler A. Testosterone therapy for men at risk for or with history of prostate cancer. Curr Treat Options Oncol. 2006 Sep;7(5):363-9

Studies with no association between serum androgen levels and prostate disease, including cancer

Studies with no significant difference in plasma testosterone and/or DHT and/or androstanediol glucuronide between prostate cancer patients and controls


Studies that show that the serum level of testosterone is not significantly associated with overall survival or serum PSA changes in castration-resistant regional (metastatic) prostate cancer


Studies with no correlation between serum testosterone and serum PSA


Studies that show that there is no association between testosterone levels and prostate cancer stage (the progression of prostate cancer does not depend on testosterone)


A study with no correlation between serum testosterone and prostate tumor volume, weight or Gleason score


A study where therapeutic androgen deprivation (blockade) has no beneficial effect on the evolution of the prostate cancer


A study with no significant association of serum testosterone with benign prostate hyperplasia

16
Studies where testosterone/androgen treatments of men with prostate cancer has no adverse effect on the progression or recurrence of the cancer, but improves quality of life and overall healthy

Studies of testosterone treatment of men with non active or cured prostate cancer

258. Morales A, Black AM, Emerson LE. Testosterone administration to men with testosterone deficiency syndrome after external beam radiotherapy for localized prostate cancer: preliminary observations. BJU Int. 2009 Jan;103(1):62-4 (n = 5; "Men with testosterone deficiency syndrome after external beam radiotherapy for localized prostate cancer are candidates for testosterone therapy .no adverse effects from testosterone supplementation")

259. Sarosdy MF. Testosterone replacement for hypogonadism after treatment of early prostate cancer with brachytherapy. Cancer. 2007 Feb 1;109(3):536-41 (n = 31; For patients with low serum testosterone levels and symptoms of hypogonadism, testosterone therapy may be used with caution and close follow-up after prostate brachytherapy)

260. Agarwal PK, Oefelein MG. Testosterone replacement therapy after primary treatment for prostate cancer. J Urol. 2005 Feb;173(2):533-6 (n = 10 hypogonadal men treated with radical retropubic prostatectomy for organ confined prostate cancer: testosterone replacement therapy can be administered carefully and with benefit to hypogonadal patients with prostate cancer)

Studies of testosterone treatment of men with active prostate cancer


263. Kaufman JM, Graydon RJ. Androgen replacement after curative radical prostatectomy for prostate cancer in hypogonadal men. J Urol. 2004 Sep;172(3):920-2 (n = 7; Each man was treated with an androgen preparation. After variable followup periods no biochemical or clinical evidence of recurrence was found in any of the group)

Anecdotal studies that show that testosterone treatment of prostate cancer patients did not accelerate the cancer progression

264. Morgentaler A. Two years of testosterone therapy associated with decline in prostate-specific antigen in a man with untreated prostate cancer. J Sex Med. 2009 Feb;6(2):574-7 ("A decline in PSA was noted in a man with untreated PCa who received T therapy for 2 years")


Studies where testosterone/androgen treatments had no adverse effect on the risk of prostate disease, including the risk of prostate cancer

Small clinical studies of androgen treatment of prostate cancer patients, performed before the days of PSA, where the androgen treatment did not stimulate the growth of the prostatic tumor and in some cases even inhibited or slowed down the growth of the tumor; the responses were extremely variable


Studies where testosterone treatment had no significant effect on PSA and/or prostate volume

273. Rhode EL, Morgentaler A. Influence of demographic factors and biochemical characteristics on the prostate-specific antigen (PSA) response to testosterone replacement therapy. Int J Impot Res. 2005 Sep 22; (No statistical increase: average = 0.31 ng/ml after 1 year of treatment of hypogonadal men)


A study where dihydrotestosterone treatment had no significant effect on serum PSA


Studies where testosterone treatment increases the serum PSA but normalizes it in patients with initial atrophic prostate bringing it up to normal levels without any excessive increase


Testosterone treatment does not increase the incidence of prostate disease


A study where previous testosterone propionate treatment (terminated 1 to 7 years before the study) did not increase the risk of prostate hypertrophy or palpable prostate irregularities in men over 45 years, whatever the treatment length or dose


Studies where DHT treatment had no effect on the prostate volume


Preconceived idea that adult growth hormone therapy avoidance based on the belief that growth hormone causes cancer

Human studies reporting higher serum IGF-1 levels in cancer

Higher IGF-1 levels in lung cancer


Higher IGF-1 levels in gastric cancer


Higher IGF-1 levels in breast cancer: several studies, including:


296. Li BD, Khosravi MJ, Berkel HJ, Diamandi A, Dayton MA, Smith M, Yu H. Free insulin-like growth factor-I and breast cancer risk. Int J Cancer 2001 Mar 1;91(5):736-9 (The odds ratios for breast cancer patients having high plasma IGF-I ≥ median) after adjusting for menopausal status and IGFBP-3 were 2.00 (p < 0.376) for total IGF-I and 6.31 (p ≤ 0.047) for free IGF-I. A high ratio of IGF-I to IGFBP-3 was also associated with breast cancer (p < 0.05)


298. Bohike K, Cramer DW, Trichopoulos D, Mantzoros CS. Insulin-like growth factor-I in relation to premenopausal ductal carcinoma in situ of the breast. Epidemiology 1998 Sep;9(5):570-3 (Women in the highest two tertiles of IGF-I and the lowest tertile of IGFBP-3 were at notably higher risk than women in the lowest tertile of IGF-I and the highest two tertiles of IGFBP-3 (odds ratio = 3.7; 95% CI = 1.1-12.2)

In acromegaly the incidence of cancer other than gastrointestinal cancer does not seem to be increased

299. Cohen P, Clemmons DR, Rosenfeld RG. Does the GH-IGF axis play a role in cancer pathogenesis? Growth Horm IGF Res. 2000 Dec;10(6):297-305. Department of Pediatrics, Mattel Children’s Hospital, UCLA, Los Angeles, CA 90095-1752, USA. hassy@mednet.ucla.edu

Increased incidence of esophagus, stomach and colon cancer


High levels in prostate cancer


Arguments contra GH use:

GH levels: Studies where positive associations between higher serum GH and/or IGF-1 levels and an increased risk of prostate or breast cancer

Studies where a higher serum IGF-1 and/or high IGF-I to IGFBP-3 molar ratio was found associated with an increased risk of prostate cancer (critics: the increased IGF-1 may be due to local production of IGF-1 by the tumour and may thus be a marker, and not a cause of cancer, or a bias due to nutritional factors - see further)

Studies where a higher serum GH was found associated with an increased risk of breast cancer (critic: based on the measurement of the daytime serum GH level, which is not representative of GH 24-hour secretion)


Studies where a higher serum IGF-1 or IGF-1/IGF-BP-3 ratio is found associated with an increased risk of breast cancer, in particular in women with ≥ 19 CA repeats in IGF-1 gene


A study where a lower serum IGF-BP-3 was found in breast cancer patients


A study where a higher serum IGF-1 / IGF-BP-3 was found associated with an increased colon cancer risk (the colon cancer risk was 4 times increased only for subjects in the upper tertile of IGF-1 and lower tertile of IGF-BP-3; for other tertiles or a combination of tertiles there was: no significant association)


In acromegaly, the incidence of and/or mortality from digestive cancer is increased


Critics: In acromegaly the GH production is 10 to 100 times the normal production, 10 to 300 times the daily doses used in GH therapy. The pituitary GH-secreting tumor in the sella turcica crushes down the production of other pituitary hormones such as ACTH, LH, FSH, TSH, creating a polyhormonal deficit: hypothyroidism, hypogonadism, hypocorticism, ..., endocrine conditions that increase the risk of glucose intolerance and diabetes. These conditions are not found in corrective GH treatment of GH deficiency.

314. van den Berg G, Frolich M, Veldhuis JD, Roelfsema F. Growth hormone secretion in recently operated acromegalic patients. J Clin Endocrinol Metab. 1994 Dec;79(6):1706-15 (Patients with active acromegaly ...secretion rate per 24 h was 25 x greater in female acromegalics & 100 x greater in male acromegalics than that in the controls.)

315. Lambert RP, Jackson IM. Investigation of hypothalamic-pituitary disease. Clin Endocrinol Metab. 1983 Nov;12(3):509-34 (In patients with large macroadenomas pituitary hormone deficiencies are almost invariable with GH and FSH/LH being the most commonly affected, followed by TSH and ACTH in that order.)


GH treatment with human pituitary GH hormone
A study where the use of human pituitary GH as therapy to GH-deficient patients treated during childhood and early adulthood up to 1985 was associated with an increased risk of colon cancer and overall cancer mortality (critics: the data are based on patients having taken GH extracted from human cadavers, now only biosynthetic growth hormone is used; moreover, the doses used in childhood are extremely high – at least seven times those used in treatment of GH-deficiency in adults)


Neutral information and alternative explanations on a possible GH and cancer relation

Possible bias in the studies with increased prostate and breast cancer risk:

Bias 1: The diagnosis of cancer may be more rapidly made in patients with high IGF-1 because they may undergo more intensive scrutiny: As raised IGF-1 may cause tissue hyperplasia, including increase in size of prostate and breast tissue, the existence of these bigger tissues and possibly of the symptoms they may cause, may lead to more intensive scrutiny, from increased rate of PSA, CEA or C1.25 measurements, to ultrasound and RX examinations, prostate or breast biopsies, and thus an increased rate of detection of very slow, asymptomatic prostate or breast cancers that would have remained undiagnosed or diagnosed much later in patients with low IGF-1. Such higher rate of cancer detection may be particularly the case for prostate cancer, where the number of detected prostate cancer cases is very low compared to the total number of cases found at autopsy, and premenopausal breast cancer patients who were diagnosed within the 2 years after the first blood sample.


Higher levels of IGF-1 or GH or acromegaly have been associated with benign prostatic hyperplasia, but not necessarily with prostate cancer


GH and IGF-1 treatment of primates can increase breast hyperplasia, not specifically breast cancer


Bias 2: After adjustment for prostate volume, no longer significant associations between serum IGF-1 and prostate cancer risk may persist (Serum IGF-1 is not useful for diagnosis of prostate cancer, but a marker of benign prostate hyperplasia and enlargement) 


Bias 3: Serum IGF-1 may actually be a surrogate marker of nutritional factors that may increase the cancer risk such as meat and milk intake (persons who eat a lot of protein, especially red meat, have higher IGF-1 levels and an increased cancer risk)


Link between meat, milk and/or protein intake, and prostate or breast cancer


Red meat and milk intake is correlated with high IGF-1


Bias 4: The increases of serum IGF-1 may be produced by the malignant tumour and constitute a consequence and not a cause as suggested in some animal studies.


Bias 5: the variability of serum IGF-1 may increase if two weeks after the initial blood test another measurement of IGF-1 was done, the results of the studies would have been different (about 40% of participants of the study would have switched from one quartile to the other)


Arguments pro GH use:

Human studies reporting no association of serum IGF-1 levels with cancer: many studies, including

Prostate cancer


Colorectal cancer


Breast cancer


Inverse (protective) associations of serum GH/IGF-1 levels and overall cancer risk

Untreated GH deficient patients have an increased overall cancer incidence (2x the normal incidence) and cancer mortality (4x)


A high serum IGF-1 is found associated with a lower risk of prostate cancer


Human study reporting greater malignancy of breast cancer in women with low IGF-1 levels


Human study reporting a lower number of IGF-1 receptors in cancer, suggesting the lack of IGF-1 effects may contribute to the disease: Markedly lower number of IGF-1 receptors in breast cancer tissue, suggesting an IGF-1 resistance (similar to insulin resistance)


No significant association between serum IGF-1 and prostate cancer:

GH therapy increases serum IGF-BP-3, which may protect against cancer: IGFBP-3 causes apoptosis of cancer cells and inhibits IGF action on cancer cells in vitro => Serum IGFBP-3 is in general negatively correlated with the cancer risk: the higher IGF-BP-3, the lower the cancer risk


A high serum IGF-BP-3 is associated with a reduced prostate cancer risk (~30%), and/or prostate cancer recurrence


Long-term GH replacement (60 months) reduced the increased cancer risk and mortality of GH deficient patients by half

Cancer mortality: reduction with GH treatment in GH-deficient adults

Cancer incidence: growth hormone therapy does not increase the risk of cancer in GH-deficient adults

Gastrointestinal cancer recurrence and mortality: non significant reduction with growth hormone therapy

Brain tumors: reduction in brain tumor recurrence and mortality in children

Pituitary adenomas: no increase in tumor progression with growth hormone treatment

GH or IGF-1 therapy to animals with cancer: may reduce the tumour incidence and/or progression

Combined GH- insulin therapy reduced the development of mammary carcinoma in female rats

GH-therapy reduced the development of lung metastases in rats with prostate cancer

A lower serum GH level is found in gastric cancer patients

GH-therapy inhibits the development of liver cancer due to carcinogens ( aflatoxin B1 or N-OH-acetylaminofluorene) in male rats

IGF-1-therapy preserved lean mass in rats with sarcoma and cachexia
No significant associations of serum levels and prostate cancer risk

No difference in plasma GH or IGF-1 between prostate cancer patients and controls


370. Cutting CW, Hunt C, Nisbet JA, Bland JM, Dalgieish AG, Kirby RS. Serum insulin-like growth factor-1 is not a useful marker of prostate cancer. BJU Int. 1999 Jun;83(9):996-9

371. Ismail HA, Pollak M, Behlouli H, Tanguay S, Begin LR, Aprikian AG. Serum insulin-like growth factor (IGF)-1 and IGF-binding protein-3 do not correlate with Gleason score or quantity of prostate cancer in biopsy samples. BJU Int. 2003 Nov;92(7):699-702


In acromegaly, the incidence of cancer, other than possibly colon cancer, does not appear to be significantly increased: in one study it was even significantly reduced by -14 %. Overall mortality is normal for patients with low posttreatment GH, but increased for patients with high posttreatment GH.


377. Orme SM, McNally RJ, Cartwright RA, Belchetz PE. Mortality and cancer incidence in acromegaly: a retrospective cohort study. United Kingdom Acromegaly Study Group. J Clin Endocrinol Metab. 1998 Aug;83(8):2730-4 (“The overall cancer incidence rate was 24 % lower than that in the general population of the U.K.; the overall cancer mortality rate was not increased, but the colon cancer mortality rate was increased.”)

No difference in serum IGF-1 between breast cancer patients and controls


GH transgenic mice with high serum IGF-1 do not develop breast, prostate, or colonic malignancies


Preconceived idea that female hormone therapy avoidance based on the belief that even bio-identical female hormones in right amounts cause breast cancer

Arguments not to treat with female hormones
Female hormones might increase the risk of breast cancer

In vitro study where non-bioidentical conjugated estrogens excessively stimulate epithelial proliferation in breast tissue, an effect worsened with the addition of medroxyprogesterone acetate (MPA)

382. Hofseth LJ, Raafat AM, Osuch JR, Pathak DR, Slomski CA, Haslam SZ. Hormone replacement therapy with estrogen or estrogen plus medroxyprogesterone acetate is associated with increased epithelial proliferation in the normal postmenopausal breast. J Clin Endocrinol Metab. 1999 Dec;84(12):4559-65.

In vivo studies where associations of oral, non-bio-identical (conjugated or other) estrogens with non-bio-identical progestogens were associated with an increase in risk of breast cancer


In vivo studies where associations of estrogens with progestogens were associated with an increase in risk of breast cancer in women with familial breast cancer

390. Steinberg KK, Thacker SB, Smith SJ, Stroup DF, Zack MM, Flanders WD, Berkelman RL. A meta-analysis of the effect of estrogen replacement therapy on the risk of breast cancer. JAMA 1991 Apr 17;265(15):1985-90 (higher risk of breast cancer in women with familial history of breast cancer if ever use of estrogen therapy; cirlic: other studies have shown that estrogen replacement did not induce a greater risk of breast cancer, but did reduce the overall mortality of women with familial history of breast cancer, see further)

Studies, which suggest indirectly that high levels of estradiol, endogenously or with oral use might increase the risk of breast cancer

A high urinary excretion of 16-alpha-OH-estrone is associated with increased risks of mammary hyperplasia and breast cancer


Treatments with oral estradiol cause a major increase in urinary 16-alpha-OH-estrone, not the case with transdermal estradiol


Treatments with oral estrogens induce supraphysiological increases in estrone sulphate and estrone serum levels, not the case with transdermal estradiol


Studies where treatments with progestogens that have a NON-BIO-IDENTICAL STRUCTURE may increase the possibility of breast cancer development

Some progestins (pregnanes) derived from progesterone stimulate apoptosis leading to breast cancer cell death; most cannot stimulate breast cancer cell multiplication; others such as estranes or gonanes derived from testosterone, stimulate breast cell multiplication in vitro through an estrogen receptor-mediated pathway


Progestogens have adverse effects on the cardiovascular system
Treatments with structurally modified progestogens block the beneficial effects of estrogens on the cardiovascular system (not the case with natural progesterone)


401. Williams JK, Hall J, Anthony MS, Register TC, Reis SE, Clarkson TB. A comparison of tibolone and hormone replacement therapy on coronary artery and myocardial function in ovariectomized atherosclerotic monkeys. Menopause. 2002 Jan-Feb;9(1):41-51


Treatments with MPA have adverse effects on cardiovascular parameters, increasing the serum triglycerides


Treatments with MPA have adverse effect on coronary arteries, increasing arteriosclerosis (not the case with bio-identical progesterone)


Treatments with MPA stimulate atheroma development (no effect of norethisterone)


Treatments with structurally modified progestogens may stimulate vasospasm of the coronary arteries (not the case with natural progesterone)


Progestins increase the risk of venous thrombo-embolic events, but increase is small compared to the other benefits


Studies that contest the validity of the above-mentioned studies of breast cancer associations with the use of non-bio-identical estrogens and progestogens


Post-WHI studies (double-blind placebo-controlled trial) are reassuring for the cardiac risks (except not for use of synthetic medroxyprogesterone acetate and therapies must cyclically be interrupted and lower doses to women with metabolic syndrome)

Use of conjugated estrogens alone by postmenopausal women with hysterectomy does not affect the incidence of coronary heart disease


Use of conjugated estrogens alone by postmenopausal women with hysterectomy: reduced coronary calcifications


No increased risks of coronary heart disease in (except increase stroke risks when oral conjugated estrogens are given alone) and metabolic syndrome is present

424. Gurney EP, Nachtigall MJ, Nachtigall LE, Naftolin F. The Women's Health Initiative trial and related studies: 10 years later: a clinician's view. J Steroid Biochem Mol Biol. 2014 Jul;142:4-11. (data supporting the use of HT administered to postmenopausal women, showing it to have more benefit than risk for symptom control, prevention of bone mineral loss and fracture, and improvement of the metabolic profile in women who began HT when they were less than 60 years of age and had their last menstrual period less than ten years previous. In hysterectomized women treated with estrogen only, a reduction in breast cancer risk was noted in all age groups.)

Use of oral conjugated estrogens and medroxyprogesterone acetate by postmenopausal women has a doubling of the cardiac risk in women with metabolic syndrome


**Oral medroxyprogesterone acetate causes cardiac isks**


**Use of oral conjugated estrogens alone by postmenopausal women increased the risk of stroke**


**Use of conjugated estrogens alone by postmenopausal women with hysterectomy does not affect the incidence of breast cancer (trend to reduction) but increased mammogram abnormalities**

429. Stefanick ML, Anderson GL, Margolis KL, Hendrix SL, Rodabough RJ, Paskett ED, Lane DS, Hubbell FA, Assaf AR, Sarto GE, Schenken RS, Yasmeen S, Lessin L, Chlebowski RT; WHI Investigators. Effects of conjugated equine estrogens on breast cancer and mammography screening in postmenopausal women with hysterectomy. JAMA. 2006 Apr 12;295(14):1647-57. (Treatment with CEE alone for 7.1 years does not increase breast cancer incidence in postmenopausal women with prior hysterectomy. However, treatment with CEE increases the frequency of mammography screening requiring short interval follow-up.)

The combination of conjugated estrogens and medroxyprogesterone acetate should have been given cyclically and not continuously


**Studies that inform that most adverse effects (increased risk of breast cancer and adverse cardiovascular effects) are due to the use of structurally NON BIO-IDENTICAL female hormones and their administration through the oral route estrogens (rather than transdermal)**

**Studies with NON BIO-IDENTICAL (foreign-to-the-human-body structure)**

2a) Absorption of non-bio-identical estrogens provides abnormal estrogens in the blood:

**Treatments with equine estrogens (the Prempro of the WHI and Million Women studies) supply the blood with abnormal estrogens.** Equine estrogens contain estrone sulfate (53-61%), equilin sulfate (23-30%) equilenin, 17 a-dihydroequilenin, 17 alpha-estradiol, 17 a-dihydroequilin and numerous other horse estrogens


**Treatments with ethinylestradiol (the Million women study):**


2b) Non-bio-identical hormones are almost always provided through the ORAL ROUTE, which is not the best route, nor a totally safe one:

2b) **Treatments with oral estrogens provide imbalanced serum levels of estrogens and urinary levels of estrogen metabolites (an abnormally high serum estrone level and an abnormal increase of urinary 16-alpha-hydroxy-estrone)**
2b-2) Treatments with oral estrogens excessively increase the serum levels of the plasma binding proteins

How? Oral estrogens, after absorption in the intestinal tract, are transported to the liver where they produce under this “estrogen dominance” excessive amounts of hormone plasma binding proteins, resulting in high serum levels of the plasma binding proteins, which bind greater amount of various hormones in the serum, thus reducing the amount of hormones bioavailable for the target cells.

2-b-3) Treatments with oral estrogens reduce the levels and activities of other hormones

Treatments with oral estrogens reduce serum IGF-1 levels and thus GH metabolic activity


Janssen YJ, Helmerhorst F, Frollich M, Roelfsema F. A switch from oral (2 mg/day) to transdermal (50 µg/day) 17beta-estradiol therapy increases serum insulin-like growth factor-I levels in recombinant human growth hormone (GH)-substituted women with GH deficiency. J Clin Endocrinol Metab. 2000 Jan;85(1):464-7


Treatments with oral estrogens reduce the excretion of melatonin metabolites and thus melatonin activity


Treatments with oral estrogens reduce serum free thyroid hormones, in particular serum free T3, and thus thyroid activity


Treatments with oral estrogens reduce cortisol levels, and thus glucocorticoid activities


Treatment with oral estrogens reduce free and total testosterone, DHT, DHEA, free cortisol, and thus androgen and glucocorticoid activities

2-c) Non-bio-identical hormones such as those of oral birth-control pills may not be better through the transdermal route (as transdermal patches): They cause similar and on some points worse adverse effects than through the oral route.

- They increase similarly or even to a greater extent the levels of the plasma binding proteins
- They may cause similar or even to a greater extent reductions of hormone activities

2c-1) The transdermal contraceptive patch (Ortho Evra/Evra, 1 patch per week of 20 µg ethinyl estradiol with 150 µg norelgestromin, the active metabolite of the progestogen norgestimate, structurally related to 19-nortestosterone)

The transdermal contraceptive patch provides higher levels of ethinylestradiol and SHBG, than the oral pill, but similar increase of on CBG

2c-2) Other transdermal contraceptive patch: ethinylestradiol/gestodene (9 mg ethinylestradiol and 1.9 mg gestodene)

2c-3) The vaginal contraceptive ring (Nuvaring, 1 per 3 weeks; 2.7 mg of ethinylestradiol and 11.7 mg of etonogestrel, which supply 12 µg of etonogestrel and 15 µg of ethinylestradiol per day) supplies much less ethinylestradiol to the body

2c-4) Other transdermal contraceptive patch: ethinylestradiol/gestodene (9 mg ethinylestradiol and 1.9 mg gestodene)
2d) Studies where oral and/or structurally non-bio identical estrogen treatments were associated with adverse effects on the cardiovascular system

Treatments with oral estrogens, including conjugated estrogens, disturb blood coagulation:

**Treatments with oral estrogens increases factor VII activity**


**Treatments with oral estrogens reduce tissue factor pathway inhibitor, a major inhibitor of the extrinsic coagulation pathway, and increase C-reactive protein, a component of the acute phase**


**Treatments with high doses of oral estrogens significantly increase serum alpha 1-antitrypsin and plasminogen levels**


**Treatments with oral estrogens significantly reduce antithrombin III and protein S activities**


**Treatments with oral estrogens increase in matrix metalloproteinase-9 within the vessel wall: could digest and weaken fibrous caps of vulnerable plaques, thus provoking thrombosis**


**Treatments with oral estrogens increase the risk of venous thromboembolism, especially during the first year**


**Treatments with oral estrogens increase the risk of ischaemic stroke among postmenopausal women**


**Treatments with oral estrogens and tibolone significantly increase serum CRP, while transdermal estradiol has no significant effect on serum CRP**


Arguments to treat with female hormones

Neutral or protective effects of female hormones on the risk of breast cancer

1g) Study where treatments with parenteral (especially transdermal) BIO-IDENTICAL estradiol proved to be safer than oral estradiol

Study where treatments with intravenous estradiol stimulate less tumour development than oral estradiol in animals
3) Studies where structurally BIO-IDENTICAL, especially TRANSDERMAL, estradiol treatment was shown to be safer for the breast from the cancer perspective than treatments with non-bio-identical estrogens

EXOGENOUS BIO-IDENTICAL ESTRADIOL

In vitro study where a treatment with estradiol provided less epithelial proliferation than with conjugated estrogens in breast tissue, addition of bio-identical progesterone was even more reassuring as it greatly reduced the moderate bio-identical estradiol-induced proliferation

A study where the treatments associating transdermal estradiol to a progestogen other than MPA do not significantly increase the breast cancer risk (83% of participants took transdermal estradiol and other progestins than MPA were used)

ENDOGENOUS BIO-IDENTICAL ESTRADIOL: Studies where high levels of endogenous estrogens are associated with less breast cancer or longer survival after breast cancer

A study where a high level of bio-identical estradiol at the moment of tumour surgery is associated with a better prognosis

Studies where increased levels of bio-identical estrogens (such as those found in mature young women compared to the levels of girls before puberty) are associated with a lower cancer mortality

Studies where a high level of estriol compared to estrone and estradiol may be associated with a reduced incidence of breast cancer


Studies where breast cancer tumours rich in estrogen receptors (that thus responds well to estrogens) had a better prognosis (more differentiated, less malignant tumour)


Treatments with transdermal estradiol alone or combined to a synthetically modified progestin increases the BC risk, but combined to bioidentical progesterone causes a -10% decrease of the breast cancer risk


5-2) ENDOGENOUS BIO-IDENTICAL PROGESTERONE:

Studies where lower endogenous BIO-IDENTICAL progesterone levels are associated with a lower overall or breast cancer incidence


Studies where the prognosis is better when the breast cancer tumour is surgically removed in the luteal phase (particularly rich in progesterone)


Studies where the presence of mastalgia, breast cysts or uterine fibroids, conditions generally related to lower progesterone levels, is associated with an increased risk of breast cancer


Neutral or protective effects of female hormones on the cardiovascular system

1g) Study where treatments with parenteral (especially transdermal) BIO-IDENTICAL estradiol proved to be safer than oral estradiol

1h) Studies where bio-identical and parenteral, in particular transdermal, estrogen treatments were associated with beneficial cardiovascular effects: more efficient and safer

Studies where low bio-identical estradiol levels are found in premenopausal women with coronary heart disease


2) Studies with beneficial cardiovascular effects of estrogen therapy, generally obtained with the use of transdermal and bio-identical estradiol

Treatments with transdermal estradiol cause vasodilatation of the brachial and forearm arteries in postmenopausal women


Treatments with oral estradiol causes vasodilatation of the brachial artery in postmenopausal women


Treatments with intracoronary or intravenous estradiol cause vasodilatation and increased distensibility of coronary arteries


Treatments with subcutaneous implants of 17-beta estradiol reduce coronary artery disease in female monkeys


Treatments with subcutaneous injections of 17-beta-estradiol protect dogs against myocardial ischemia


Treatments with intravenous 17-beta-estradiol protect cats against acute myocardiac ischemia

Treatments with transdermal estrogen reduce angina in postmenopausal women with angina and normal coronary arteries


Treatments with implants of estradiol protect arteries of rats against atherosclerosis: prevent LDL-binding to arterial wall, reduce endothelial layer permeability


Overview on vascular protective effects of estrogen


Treatments with oral estradiol cause vasodilatation and increased distensibility of arteries


Treatments with transdermal estradiol reduce the carotid artery wall thickness and thus atherosclerosis in postmenopausal women


Treatment with transdermal estradiol treatments have no adverse effects on hemostatic factors and other cardiovascular risk factors (no CRP increase e.g.), while oral estrogen treatments do


Studies with beneficial or neutral effects of BIO-IDENTICAL PROGESTERONE on the cardiovascular system

Treatment with vaginal progesterone gel delays exercise-induced myocardial ischemia in postmenopausal women with coronary heart disease and/or previous myocardial infarction

Treatments with transdermal or intravenous progesterone (4 weeks) protect against severe prolonged coronary vasoconstriction, and reduce lipoprotein (a) in non and preatherosclerotic and atherosclerotic female monkeys

Treatments with intravenous progesterone increase coronary blood flow in pigs

Treatments with progesterone in vitro relax isolated animal coronary smooth muscles cells and arteries

Treatments with progesterone have no negative effect on estradiol-induced protection of coronary arteries

Preconceived idea that cortisol and glucosteroid therapy avoidance based on the belief that side effects are unavoidable with its use

Excessive doses of glucocorticoids (40-60 mg/day of cortisol or > 7.5 mg/day of prednisolone) suppress endogenous cortisol secretion and it take may up to 8 months on average to recover initial endogenous cortisol secretion after discontinuation of treatment (recovery is especially long if synthetic derivatives of cortisone at very high doses have been used)

1) 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


566. 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*)


**Supraphysiological/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 are 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

569. 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 partial


**Studies with adverse effects of glucocorticoid treatment on bone density:**

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


Studies where the use of glucocorticoids was associated with a reduction of bone density (*Critics: the treatments were not counterbalanced by a supplement of anabolic hormones such as DHEA, androgen or female hormone or calcitonin therapy*)
578. 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)


580. 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%”; Critics: 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)

581. 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)

582. 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)

583. 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 offset by post-menopausal estrogen replacement therapy)

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.


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

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


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


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


40
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

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

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


Studies with no effect of glucocorticoid treatment on bone density: studies with up to 58 months of treatment and 6 mg/day of methylprednisolone

592. 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 methylprednisolone for 12-58 months: absence of quantitative bone mass reduction and normal corticosterone reserve were observed even after 58 months of daily steroid administration”)

593. 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


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


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

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

With DHEA:

596. Papiserska L, Rabijewski M, Kasperlik-Zaluska A, Zgliczyński W. Effect of DHEA supplementation on serum IGF-1, osteocalcin, and bone mineral density in postmenopausal, glucocorticoid-treated women. Adv Med Sci. 2012 Jun 1;57(1):51-7. (19 women, aged 50-78 years, treated at least for three years with average daily doses of more than 7.5 mg prednisone. A significant increase of bone mineral density in the lumbar spine and femoral neck was observed after six and twelve months of DHEA treatment.)

597. Sánchez-Guerrero J, Fragoso-Loyo HE, Neuwelt CM, Wallace DJ, Ginzler EM, Sherrer YR, McLlwaan HH, Freeman PG, Aranow C, Petri MA, Deodhar AA, Blanton E, Manzi S, Kavanagh A, Lisse JR, Ramsey-Goldman R, McKay JD, Kivitz AJ, Mease PJ, Winkler AE, Kahl LE, Lee AH, Furie RA, Strand CV, Lou L, Ahmed M, Quares B, Schwartz KE. Effects of prasterone on bone mineral density in women with active systemic lupus erythematosus receiving chronic glucocorticoid therapy. J Rheumatol. 2008 Aug;35(8):1567-75. (155 patients with SLE received 200 mg/day prasterone or placebo for 6 months in a double-blind phase, there was a trend for a small gain in BMD at the L-spine for patients who received 200 mg/day prasterone for 6 months versus a loss in the placebo group (mean +/- SD, 0.003 +/- 0.035 vs -0.005 +/- 0.053 g/cm(2), respectively; p = 0.293 between groups).)
With calcitonin


With female hormone replacement


With GH


605. 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 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)


With vitamin D


With biphosphonates


With sodium fluoride

Exercise

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.

Universities with postgraduate education programs in anti-aging medicine for physicians

Actual:
621. USA: American academy of anti-aging medicine’s in fellowship in metabolic and nutritional-medicine (previously fellowship in regenerative and functional medicine (patterned with the George Washington University and the University of South Florida): http://www.mmimedicine.com/fellowship-in-metabolic-and-nutritional-medicine.html
625. Thailand: Master of Science Programme in Anti-Aging and Regenerative Medicine at Mae Fah Luang University: http://www.mfu.ac.th/school2013/anti-aging/#
627. Brazil: Post Graduation Lato Sensu Master of Science on Human Physiology at Talles de Mileto College (Sao Paulo) http://emec.mec.gov.br/emec/consulta-cadastro/detalhamento/d96957455f6405d14c6542552b0f6eb/MTY5NDM=/93916316abe23148507bd4c260e4b878/MzEDNjE= (360h, 18 monthslong)

Previous, not valid anymore university postgraduate formation in anti-aging medicine for physicians:

Not bound to university

Placebo-controlled studies with recombinant human growth hormone: 507

Growth hormone therapy on healthy young and middle-aged adults: 65 placebo-controlled studies


Growth hormone therapy on healthy elderly adults: 21 placebo-controlled studies


699. Sattler FR, Castaneda-Sceppa C, Binder EF, Schroeder ET, Wang Y, Bhasin S, Kawakubo M, Stewart Y, Yarasheski KE, Ulloor J, Colletti P, Roubenoff R, Azen SP. Testosterone and growth hormone improve body composition and muscle performance in older men. J Clin Endocrinol Metab. 2009 Jun;94(6):1991-2001 (122 community-dwelling men 70.8 +/- 4.2 yr of age with BMI of 27.4 +/- 3.4 kg/m2, testosterone of 550 ng/dl or less, and IGF-I in lower adult tertile (< or = 167 ng/dl) were randomized to receive transdermal testosterone (5 or 10 g/d) during a Leydig cell clamp plus GH (0.3, or 5 mg/kg, d) for 16 wk.) Total lean body mass increased (1.0 +/- 1.7 to 3.0 +/- 2.2 kg) as did appendicular lean tissue (0.4 +/- 1.4 to 1.5 +/- 1.3 kg), whereas total fat mass decreased by 0.4 +/- 0.9 to 2.3 +/- 1.7 kg as did trunk fat (0.5 +/- 0.9 to 1.5 +/- 1.0 kg) across the six treatment groups and by dose levels for each parameter (P < or = 0.0004 for linear trend). Composite maximum voluntary strength of upper and lower body muscles increased by 14 +/- 34 to 35 +/- 31% (P < 0.003 in the three highest dose groups) that correlated with changes in appendicular lean mass. Aerobic endurance increased in all six groups (average 96 +/- 137 sec longer). Systolic and diastolic blood pressure increased similarly in each group with mean increases of 12 +/- 14 and 8 +/- 8 mm Hg, respectively. Other predictable adverse events were modest and reversible. Fasting blood sugar increased by 3 +/- 0.56 mmol/liter; P = 0.002) across the entire study population but did not reach Bonferroni-adjusted significance (P < 0.008) in any of the six groups (supplemental Table 1). HOMA-IR and QUICKI, indices of insulin resistance, changed minimally but were likewise unchanged in each of the six groups.)


**Growth hormone therapy on GH deficient adults:** 169 placebo-controlled studies


Christ ER, Cummings MH, Westwood NB, Sawyer BM, Pears E, Stönsken PH, Russell-Jones DL. The importance of growth hormone in the regulation of erythropoiesis, red cell mass, and plasma volume in adults with growth hormone deficiency. J Clin Endocrinol Metab. 1997 Sep;82(9):2985-90.


Growth hormone therapy on adults with disorder: 207 placebo-controlled studies

Obesity - adults


### Prader-Willi syndrome - adults


Type 2 Diabetes & obese - adults


Impaired glucose tolerance - adults


Malnourished - adults


Anorexia Nervosa - adults


Kidney failure/hemodialysis - adults


Cardiac failure - adults


Hypercholesterolemia - adults


Burned - adults


**Surgery - adults**


analgesia and parenteral nutrition.


**Trauma - adults**


**HIV/AIDS - adults**


Moyle GJ, Daar ES, Gertner JM, Kotler DP, Melchior JC, O'Brien F + Svanberg E; Serono 9037 Study Team. Growth hormone improves lean body mass, physical performance, and quality of life in subjects with HIV-associated weight loss or wasting on highly active antiretroviral therapy. J Acquir Immune Defic Syndr.2004 Apr 1;35(4):367-75. (3 to 6 mg/day)


Infection sepsis - adults


Cancer cachexia - adults


Osteopenia, osteoporosis - adults


**Bone fractures - adults**


**Fibromyalgia rheumatoid disorder - adults**


**Psychiatric disease - adults**


**Myopathy/Neurodeg. disorders - adults**


**Liver and Crohn's disease - adults**


**Short bowel syndrome - adults**


**Respiratory diseases - adults**


**Critical Illness - adults**


**Parenteral nutrition - adults**


**OTHER: Oligospermia, hypogonadism -adults**


Poor responders to IVF (in vitro fertilization).


Turner syndrome


Growth hormone therapy on growth hormone-deficient children: 46 placebo-controlled studies (50 with mixed studies)

GH deficient - children/adolescents


Growth hormone therapy on children with disorder: 43 placebo-controlled studies (48 in total as 5 other placebo-controlled trials are with both children and adults)

Short stature - children


Burned children


Turner syndrome - children


Obesity - children

Kidney failure - children

Surgery- children

Liver and Crohn's disease – children only

Cystic fibrosis children

Edema disappears with GH dose reduction

Insulin sensitivity: greater improvement with smaller doses of GH treatment
1141. Yuen KC, Dunger DB. Persisting effects on fasting glucose levels and insulin sensitivity after 6 months of very low-dose GH therapy in adults with severe GH deficiency. Clin Endocrinol (Oxf). 2006 May;64(5):549-55 (the Low 0.1 mg/day GH dose has beneficial effects on fasting glucose levels and insulin sensitivity, which persist after 6 months of discontinuation of therapy, which high doses of 0.5 mg/day have

Viagra: first study and adverse events, including mortality and other
1143. Lowe G, Costabile RA. 10-Year analysis of adverse event reports to the Food and Drug Administration for phosphodiesterase type-5 inhibitors. J Sex Med. 2012 Jan;9(1):265-70. (10-year analysis of adverse event reports to the Food and Drug Administration .. Overall, 14,818 adverse events (AEs) were reported for sildenafil. There were 1,824 (12.3%) reported deaths, and reports of cardiovascular AEs numbered 2,406 (16.2%). … Only 10% of AE reports sent to the FDA for PDE5-i were from pharmaceutical manufacturers. Reports of deaths associated with PDE5-i remain around 5% of total reported events. …)

Testosterone therapy in men: 312 placebo-controlled studies – 303 in adults

Healthy adults
Healthy young men using testosterone for contraception (or sport abuse)


Healthy young men chemically castrated receiving testosterone


Healthy middle-age men


Healthy elderly men


Healthy elderly men chemically castrated receiving testosterone


Healthy middle-aged men ≥ age 40 with testosterone deficiency, serum testosterone level below the lower reference limit


Elderly men with serum testosterone levels near or below the lower reference limit of young men


120. Vaughan C, Goldstein FC, Tenover JL. Exogenous testosterone alone or with finasteride does not improve measurements of cognition in healthy older men with low serum testosterone. J Androl. 2007 Nov-Dec;28(6):875-82. Wesley Woods Health Center, Atlanta, GA 30329, USA


Healthy adult men of all ages with testosterone deficiency, serum testosterone level below the lower reference limit

Testosterone deficiency in adult men of all ages


Klinefelter syndrome


Somatic diseases in adult men

Heart coronary artery disease


Heart failure


163. Smith AM, English KM, Makin CJ, Jones RD, Jones TH, Channer KS. Testosterone does not adversely affect fibrinogen or tissue plasminogen activator (tPA) and plasminogen activator inhibitor-1 (PAI-1) levels in 46 men with chronic stable angina. Eur J Endocrinol. 2005 Feb;152(2):285-91.


Chronic obstructive pulmonary disease


Sleep apnea

Liver disease - alcoholic cirrhosis

Kidney failure/hemodialysis

Rheumatoid arthritis

Osteopenia, osteoporosis

Obesity

Type 1 diabetes

Type 2 diabetes


Type 2 diabetes and metabolic syndrome


Metabolic syndrome


Malnourishment in elderly men


Reduced mobility in elderly men


Ill elderly men


Surgery - pain


Surgery - recovery


HIV/AIDS


**Lack of fertility**


**Neuropsychiatric diseases in adult men**

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Cognitive impairment


Depression


Social anxiety


Schizophrenia

Drug addiction, opioid-induced androgen deficiency


Parkinson’s disease


Somatic underdevelopment in boys

Hypospadias, penis hypotrophy in boys


Puberty delay, short stature: testosterone treatment for puberty initiation and growth improvement in prepuber adolescent boys


Testosterone in women: 103 placebo-controlled studies – all in adults

Healthy women

Healthy young women


Young women undergoing in vitro fertilization procedures

Testosterone-deficient women
Women of all ages with overt testosterone deficiency of all ages, serum testosterone level below the lower reference limit

Sexual dysfunction


Women with hysterectomy with or without oophorectomy

oophorectomy: effects on sexual function, body composition, muscle performance and physical function in a randomized trial. Menopause. 2014 Jun;21(6):612-23

Cognitive dysfunction


Women with primary ovarian deficiency


Anorexia nervosa women


Lupus erythematosus


Postmenopausal women


385. Fernandes T, Costa-Paiva LH, Pedro AO, Baccaro LF, Pinto-Neto AM. Efficacy of vaginally applied estrogen, testosterone, or polyacrylic acid on vaginal atrophy: a randomized controlled trial. Menopause. 2016 Jul;23(7):792-8


**Women with HIV-AIDS**


**Cardiac failure- postmenopausal women**


**Lichen sclerosus – topical vulvar testosterone treatment**


**Thyroid treatment: 158 placebo-controlled studies (130 in adults)**
Adults

Healthy young adults: Thyroxine treatment

Healthy young adults: Triiodothyronine treatment

Healthy adults of all ages: Triiodothyronine treatment


Healthy adults undergoing space flight stimulation: Triiodothyronine treatment


Healthy adults undergoing adaptation to extreme cold (Antarctic polar environment): Thyroxine treatment


Healthy adults undergoing adaptation to extreme cold (Antarctic polar environment): Triiodothyronine treatment


Adults with a family history of thyroid disease and a serum TSH within or above the upper serum TSH limit: Thyroxine treatment


Adults of all ages with subclinical hypothyroidism (serum TSH above the upper reference limit and serum T4 within the reference range): Thyroxine treatment


Adults of all ages with overt hypothyroidism: Thyroxine treatment


Adults of all ages with overt hypothyroidism: Thyroxine or thyroxine and triiodothyronine treatment


Patients with thyroid nodules: Thyroxine treatment


Patients with endemic goitre: Thyroxine treatment


Patients after thyroidectomy: Thyroxine treatment


Adults with hypothyroid symptoms but thyroid tests within reference range: Thyroxine treatment


Adults during or after hyperthyroidism for Graves disease: Thyroxine treatment


Adults with obesity: Triiodothyronine treatment


Adults with Raynaud syndrome: Triiodothyronine treatment


Adults with heart failure: Triiodothyronine treatment


Adults with cardiac surgery Triiodothyronine treatment


Patients with asthma: Triiodothyronine treatment


Adults with kidney failure and/oronhemiodyalisis: Thyroxine treatment


Patients with burn injury: Triiodothyronine treatment
Female patients with premenstrual syndrome: Triiodothyronine treatment


Female patients with infertility and with subclinical hypothyroidism or thyroid antibody positivity undergoing In vitro fertilization: thyroxine treatment


Female patients with infertility: thyroid extract treatment


Brain dead organ donors: Triiodothyronine treatment


Patients on anti-epileptics: Thyroxine treatment


Elderly patients with dementia: Triiodothyronine treatment


Patients with depression and subclinical hypothyroidism: Thyroxine treatment


Patients with depression: Triiodothyronine treatment


Female patients with positive thyroid antibodies: thyroxine treatment to prevent postnatal depression

Patients with depression on antidepressants: Addition of triiodothyronine treatment


Patients on antidepressant therapy + T3 or thyroxine


Patients with schizophrenia: Triiodothyronine treatment


Patients with alopecia areata: Topical triiodothyronine


Thyroid hormone analog D-thyroxine

Adults with heart failure: Thyroxine treatment


Adults with dyslipidemia: D-thyroxine treatment


Adults with coronary heat disease: D-thyroxine treatment


Adults with hemorrhagic stroke: D-thyroxine treatment

**Adults with scleroderma: D-thyroxine treatment (not efficient)**


**Children**

**Fanconi anemia syndrome - children: Thyroxine treatment for growth stimulation**


**Attention deficit disorder – children: Triiodothyronine treatment**


**Autism – children: Triiodothyronine treatment**


**Down syndrome - children**


**Pre-term infants: Thyroxine treatment**


Adults

Muscle relaxation, rarely an improvement of the REM or deep sleep. Controlled studies where a significant beneficial effect of melatonin on sleep in adults was observed and 17 in children:

Melatonin: 147 placebo-controlled studies on the effect of melatonin on sleep (130 in adults): 110 placebo-controlled studies where a significant beneficial effect of melatonin on sleep in adults was observed and 17 in children: the beneficial effect mainly consists in a shortening of the time to fall asleep (quicker sleep onset) and a profound muscle relaxation, rarely an improvement of the REM or deep sleep.

Adults


Hansen MV, Madsen MT, Andersen LT, Hageman I, Rasmussen LS, Bokmand S, Rosenberg J, Gögenur I. Effect of Melatonin on Cognitive Function and Sleep in relation to Breast Cancer Surgery: A Randomized,
Melatonin - disease: a 6


584. Schwertner A, Conceição Dos Santos CC, Costa GD, Deitós A, de Souza A, de Souza IC, Torres IL, da Cunha Filho JS, Caumo W. Efficacy of melatonin in the treatment of endometriosis: a phase II, randomized, double-blind, placebo-controlled trial. Pain. 2013 Jun;154(6):874-81 (the treatment reduced daily pain scores by 39.80% (95% confidence interval [CI] 12.88-43.01%) and dysmenorrhea by 38.01% (95% CI 15.96-49.15%). Melatonin improved sleep quality, reduced the risk of using an analgesic by 80%, and reduced BNFV levels independently of its effect on pain. This)


589. Russcher M, Koch BC, Nagtegaal JE, van Ittersum FJ, Pasker-de Jong PC, Hagen EC, van Dorp WT, Gareëls B, Wildbergh TX, van der Westerlaken MM, Gaillard CA, Ter Wee PM. Long-term effects of melatonin on quality of life and sleep in hemodialysis patients (Melody study): a randomized controlled trial. Br J Clin Pharmacol. 2013 Nov;76(5):668-79. (Considering sleep, at 3 months sleep efficiency and actual sleep time had improved with melatonin compared with placebo on hemodialysis days (difference 7.6%, 95% CI 0.77, 14.4 and 49 min, 95% CI 2.1, 9.5, respectively). At 12 months none of the sleep parameters differed significantly from placebo)


595. Garlinkel D, Zorin M, Wainstein J, Matas Z, Laudon M, Zisapel N. Efficacy and safety of prolonged-release melatonin in insomnia patients with diabetes: a randomized, double-blind, crossover study. Diabetes Metab Syndr Obes. 2011;4:307-13. (Diabetes Following 5 months of prolonged-release melatonin treatment, mean HbA1c (standard deviation) was significantly lower than at baseline (9.13% ± 1.55% versus 8.47% ± 1.67%, respectively, P = 0.005).


602. Rahman SA, Kayumov L, Shapiro CM. Antidepressant action of melatonin in the treatment of Delayed Sleep Phase Syndrome. Sleep Med. 2010 Feb;11(2):131-6 (Melatonin treatment significantly reduced depression scores in the depressed patients as measured by the CES-D and Hamilton Depression Rating Scale—17. Melatonin treatment improved sleep continuity in both group)


Dawson D, Encel N, Lushington K. Improving adaptation to simulated night shift: timed exposure to bright light versus daytime melatonin administration. Sleep. 1995 Jan;18(1):11-21


Yoon IY, Song BG. Role of morning melatonin administration and attenuation of sunlight exposure in improving adaptation of night-shift workers. Chronobiol Int. 2002 Sep;19(5):903-13


19 placebo-controlled studies with no significant effect of melatonin on sleep in adults

684. Amstrup AK, Skjaer T, Moskilde L, Rejmark L. The effect of melatonin treatment on postural stability, muscle strength, and quality of life and sleep in postmenopausal women: a randomized controlled trial. Nutr J. 2015 Sep 30;14:102. (1 or 3 mg melatonin, or placebo nightly for 12 months.)


One placebo-controlled study with report of a significant adverse effect of melatonin treatment on sleep in adults.

Chen


Eckerberg B, Lowden A, Nagai R, Akerstedt T. Melatonin treatment effects on adolescent students’ sleep timing and sleepiness in a placebo-controlled crossover study. Chronobiol Int. 2012 Nov;29(9):1239-48. (Compared with PL school weeks, the students reported less wake up (p < .05), less school daytime sleepiness (p < .05) and increased evening sleepiness (p < .005) during melatonin weeks. could advance the sleep timing and make the students more alert during school days even if they continued their often irregular sleep habits during)


Aldosterone: 13 placebo-controlled trials – all in adults
**Healthy men**: IV aldosterone produces acute cardiovascular (sympathetic) effects (first 45 min after injection) and delayed (5½ - 6½ h after) increased vagal tone (parasympathetic predominance)


**Healthy men**: Aldosterone at 100 µg, tending to increase cardiac vagal activity and enhances the heart rate (tachycardia) response to diastolic blood pressure-reducing nitroprusside


**Healthy men**: Aldosterone at 3 µg /min. rapidly impairs the baroreflex response.

723. Schmidt BM, Horisberger K, Feuring M, Schultz A, Wehling M. Aldosterone blunts human baroreflex sensitivity by a nongenomic mechanism. Exp Clin Endocrinol Diabetes. 2005 May;113(5):252-6. (tachycardic response to arterial baroreceptor deactivation was more pronounced in the aldosterone experiments)

**Healthy men**: Aldosterone (+7.6%) increases blood flow by increasing NO release and at the vascular smooth muscle cells by promoting vasoconstriction of forearm arteries


**Healthy men**: IV aldosterone rapidly attenuated endothelium-dependent vasodilatation to acetylcholine (-28% less vasodilatation)

**Healthy men**: Aldosterone increases phosphocreatine recovery in muscles to significantly higher levels immediately after isometric contraction of 8 min of aldosterone administration


**Healthy men**: Aldosterone at 500 µg (pharmacological dose) slightly reduces glomerular filtration rate and with inhibition of nitric oxide synthase reduces renal blood flow, triggering a mechanism for increases in blood pressure


**Healthy men**: Aldosterone reduces the excretion of sodium and chloride and increases excretion of potassium and (net) acid in the urine


**Healthy men**: no obvious effect on sleep of aldosterone


**Patients with disease**

**Orthostatic hypotension**: Aldosterone reduces orthostatism


**Suspected coronary heart disease**: IV aldosterone at supraphysiological dose (1 mg) increases systemic vascular resistance, cardiac output, and cardiac index within 3 minutes, effect disappeared within 10 min.

**Supraventricular arrhythmias:** IV aldosterone increases monophasic action potential duration within minutes in patients


**Fludrocortisone treatment: 19 placebo-controlled studies – 17 in adults**

**Healthy adults**

**Young healthy women:** Fludrocortisone treatment produces significant suppression of CRH secretion, trend to significant reduction of secretion of ACTH and cortisol secretion from dose 75 µg/day on


**Healthy adults:** Fludrocortisone treatment produces significant effects on pituitary-adrenal axis, arterial tone and intestinal sodium excretion


**Aldosterone deficiency:** Fludrocortisone produces significantly beneficial effects (reduction of sodium excretion)


**Orthostatic hypotension:** Fludrocortisone significantly reduces orthostatic hypotension in patients


**Vasovagal syncope:** Fludrocortisone significantly reduced the likelihood of syncope in patients


**Orthostatic hypotension:** Fludrocortisone does not prevent orthostatic hypotension after space flight


**Chronic fatigue syndrome:** Fludrocortisone associated to hydrocortisone at very low doses does not significantly reduce fatigue


**Chronic fatigue syndrome:** Fludrocortisone alone does not significantly improve CFS symptoms

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**Borderline personality disorder:** Fludrocortisone at supraphysiological doses (400 μg/day) improves memory (cognitive function: verbal, visuospatial and working memory), in healthy subjects only working memory


**Borderline personality and major depressive disorders, healthy subjects:** No effect of fludrocortisone on autobiographical memory


**Severe traumatic brain injury:** Fludrocortisone associated to hydrocortisone at low doses does not significantly prevent hospital-acquired pneumonia


**Septic shock:** Fludrocortisone associated to hydrocortisone at low doses produces beneficial effects, including better renal function


**Septic shock:** Fludrocortisone associated to hydrocortisone at low doses reduces mortality


**Children**

**Children with syncope or severe presyncope:** Fludrocortisone: produces significant beneficial effects to reduce syncopal symptoms; including syncope


**Thymosin alpha 1 treatment:** 16 human placebo-controlled trials mentioned in PubMed

**Elderly men: the immune stiuluation with thymosin-alpha-1 (1 trial, 85 patients)**


**Sepsis: the improvement with thymosin-alpha-1 and ulinastatin** (increased survival, improved immune parameters)(6 trials, 915 patients)


(+ 3 other trials mentioned in meta-analysis talks of 6 trials)


758. Chronic obstructive pulmonary disease (acute exacerbation): the improvement with thymosin-alpha-1 (1 trial, 84 patients)


Chronic hepatitis B: the improvement with thymosin-alpha-1 (2 trials).


+ 3 other trials mentioned in meta-analysis:


Chronic hepatitis C: the improvement with thymosin-alpha-1 (1 trial, 103 patients)


Chronic hepatitis C: no significant improvement with thymosin-alpha-1 (1 trials, 571 patients)


Cancer (overall) after radiotherapy or chemotherapy (immune depression): trend toward improvement with thymosin-alpha-1 or thymopentin (4trials, > 100 patients)


Mentions 3 more placebo-controlled trials in review


Cancer (lung) after radiotherapy (immune depression): the improvement with thymosin-alpha-1 (2 trials, 63 patients)


Senescence is associated with a decline of most hormone levels

Senescence is associated with a decline or imbalance of most endocrine axes

Senescence is associated with a decline of the pineapple-melatonin axis

Lower nocturnal serum melatonin and lower urinary melatonin metabolite with senescence


The circadian cycle of serum melatonin is altered with senescence: reduced amplitude and phase advance


Senescence is associated with a decline of the growth hormone (GH) axis:

Senescence is associated with lower GH production


Senescence is associated with lower GH and IGF-1 levels and increased somatostatin


Senescence is associated with alterations in the circadian cycle of serum GH and its pulses of secretion: a reduced amplitude and a phase advance


Senescence is associated with reductions of the serum levels of IGF-1


Senescence is associated with a reduction of the number of IGF-1 (cellular) receptors

1167. Martineau LC, Chadan SG, Parkhouse WS. Age-associated alterations in cardiac and skeletal muscle growth factor transporters, insulin and IGF-1 receptors, and PI3-kinase protein contents in the C57BL/6 mouse. Mech Ageing Dev. 1999 Jan 15;106(3):217-32 (Cardiac (-23 to -24%) and skeletal muscle (-40 to -62%) IGF-1 receptors were decreased in adult and old animals with senescence)


Senescence is associated with a decline of the hypothalamic-oxytocin axis

Senescence is associated with an apparent maintenance in the number of oxytocin-secreting cells in humans, but a decline in animals


Senescence is associated with a decline in oxytocin secretion to stimuli


Senescence is associated with a decline in oxytocin levels


Senescence is associated with a decline in oxytocin immunoreactive neurons in the brain


Senescence does not appear to be associated with alterations of the circadian cycle of serum oxytocin (with nighttime peak at 02h)


Senescence is associated with lower oxytocin receptor levels in target cells, suggesting an age-related progressive increase in resistance to oxytocin


Senescence is associated with a decrease of the hypothalamic-vasopressin axis


Senescence is associated with no change in vasopressin levels in humans


Senescence is associated with a delayed or gradual loss of adaptation to stimuli:


1192. Fliers E, Swaab DF, Pool CW, Verwer RW. The vasopressin and oxytocin neurons in the human supraoptic and paraventricular nucleus; changes with aging and in senile dementia. Brain Res. 1985 Sep 2;2342(1):37-44

Senescence is associated with a decline in vasopressin levels in serum, suprachiasmatic nuclei and hypothalamus in rats


Senescence is associated with a gradual decrease in vasopressin levels and size of vasopressin-secreting cells up to the sixth decade, activation after age 80


Senescence is associated with a delay or gradual loss of adaptation to stimuli:

Less vasopressin is additionally secreted in reaction to exercise


Senescence is associated with an excessive and quicker increase in vasopressin level in reaction to dehydration


Senescence is associated with a decline in vasopressin receptors paralleling age-related defects in urine concentration


Senescence is associated with a decline in target cell sensitivity to vasopressin actions:

Decline or delay in vasopressin-induced renal concentrating ability


Decline in dilatation of brain arteries


Decline in behavioral and cardiovascular responses


Senescence is associated with a decline of the thyroid axis

Senescence is associated with reductions of the serum levels of TSH, T3 and T4


120. Herrmann J, Heinen E, Kroil HJ, Rudorff KH, Kruskemper HL. Thyroid function and thyroid hormone metabolism in elderly people. Low T3-syndrome in old age? Klin Wochenschr. 1981 Apr 1;59(7):315-23


Senescence is associated with a reduction of the metabolic clearance of thyroid hormones


Senescence is associated with a reduction of the amount of thyroid hormone (cellular) receptors

Senescence is associated with alterations of the circadian cycle of serum TSH:
Lower amplitude and phase advance

Senescence is associated with unfavorable changes of the calcium-parathormone axis

Senescence is associated with telomere shortening in parathyroid tissue

Senescence is associated with lower serum levels of parathormone in hemodialysis and bedridden patients

Senescence is associated with higher serum levels of Parathormone
121. Vieth R, Ladak Y, Wallfish PG. Age-related changes in the 25-hydroxyvitamin D versus parathyroid hormone relationship suggest a different reason why older adults require more vitamin D. J Clin Endocrinol Metab. 2003 Jan;88(1):185-91

Senescence is associated with a progressively (and excessively) higher secretion of parathyroid hormone in response to lower serum calcium levels

Senescence is associated with a need for progressively higher serum vitamin D3 levels and intake to reduce serum parathormone levels
127. Vieth R, Ladak Y, Wallfish PG. Age-related changes in the 25-hydroxyvitamin D versus parathyroid hormone relationship suggest a different reason why older adults require more vitamin D. J Clin Endocrinol Metab. 2003 Jan;88(1):185-91 (PTH levels of the elderly who had 25(OH)D concentrations greater than 100 nmol/liter matched PTH of younger adults having 25(OH)D concentrations near 70 nmol/liter)

High calcium intake (2.4 g/day vs 0.8 g/day) neutralizes the age-related increase in serum parathormone

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Senescence is associated with a moderate decline of the adrenal-cortisol axis


Senescence is associated with a lowering of glucocorticoid (cellular) receptors with senescence


Senescence is associated with a lowering of glucocorticoid (cellular) receptors with senescence


Increasingly greater imbalance of the anabolic/catabolic hormonal balance with senescence

115
Senescence can be associated with a higher serum cortisol in the evening and at night, and phase advance of cortisol rhythm


Senescence is associated with a decline of the adrenal-DHEA axis


1265. Birkenhäger-Gillesse EG, Derksen J, Lagaay AM. Dehydroepiandrosterone sulphate (DHEAS) in the oldest old, aged 85 and over. Ann N Y Acad Sci. 1994 May 31;719:543-52 (DHEAS levels decreased fourfold between the young adults and those aged 85 and over. In men this decrease continued after the age of 85)


The anabolic/catabolic hormone balance becomes increasingly inadequate with senescence


Senescence is associated with alterations of the circadian cycle of serum DHEA sulphate:


Senescence is associated with a decline of the adrenal-cortisol axis

Senescence is associated with a progressive decline in pregnenolone levels, especially in women

1276. Meloun M, Hill M, Vceláková-Havlíková H. Minimizing the effects of multicollinearity in the polynomial regression of age relationships and sex differences in serum levels of pregnenolone sulfate in healthy subjects. Clin Chem Lab Med. 2009;47(4):464-70 (In women, a significant maximum was found around the 30th year followed by a rapid decline, while the maximum in men was achieved almost 10 years earlier and changes were minor up to the 60th year.

Senescence is associated with a decline of the ovarian-estrogen axis

Decrease of estrogen and progesterone levels with senescence, including in women with normal cycles


1280. Cahill DJ, Prosser CJ, Wardle PG, Ford WC, Hul MG. Relative influence of serum follicle stimulating hormone, age and other factors on ovarian response to gonadotrophin stimulation. Br J Obstet Gynaecol. 1994 Nov;101(11):999-1002 (Women over 40 have a significantly lower serum oestradiol in comparison with women less than 40 years old)

1281. Sherman BM, West JH, Korenman SG. The menopausal transition: analysis of LH, FSH, estradiol, and progesterone concentrations during menstrual cycles of older women. J Clin Endocrinol Metab. 1976 Apr;42(4):629-36 (Perimenopause: shorter cycles with lower estradiol and progesterone; in women at or above age 36 years; also lower serum oestradiol at stimulation for in vitro fertilization)

Decrease of serum estradiol levels with senescence at stimulation for in vitro fertilization

1282. Lau WN, So WW, Yeung WS, Ho PC. The effect of ageing on female fertility in an assisted reproduction programme in Hong Kong: retrospective study. Hong Kong Med J. 2000 Jun;6(2):147-52 (Compared with women aged ≤ 30 years, women aged ≥ 36 years had a significantly higher cycle cancellation rate, fewer oocytes retrieved per retrieval cycle, fewer oocytes fertilised per retrieval cycle, fewer cleaving embryos per retrieval cycle, and lower serum oestradiol despite a larger amount of human menopausal gonadotrophin having been used)

Decrease in urinary progesterone metabolites with senescence


Decrease of metabolic clearance of the estrogens with senescence


A history of prior pregnancy or induced abortion is associated with a decline of the ovarian-estrogen axis


Tubal ligation is associated with a decline of the ovarian-estrogen axis
Senescence is associated with a decline of the adrenal- and ovarian-testosterone axes:

Testosterone derives in women for more than 90% from the much quicker declining androgenic hormones and arterial stiffness, based on longitudinal hormone measurements. Am J Physiol 1998;63(5):322-8

Testosterone treatment may oppose and testosterone deficiency may trigger some mechanisms of senescence in women

Immune deficiency: testosterone may improve the immune resistance in certain conditions

Senescence is associated with a decline in the pituitary-testosterone axis in men

Senescence in men is associated with a decline in testosterone levels

Senescence is associated with a decline of the serum testosterone level in women

Testosterone levels in older men: longitudinal results from the Massachusetts Male Aging Study. J Clin Endocrinol Metab. 2007 Sep;92(9):3026-32


Martínez Jabaloyas JM, Queipo Zaragoza A, Ferrandis Cortes C, Queipo Zaragoza JA, Gil Salom M, Chuan Nuez P. Changes in sexual hormones in a male Actas Urol Esp. 2008 Jun;32(6):603-10 (“Age was associated with a significant decrease (p < 0.05) in total testosterone (0.6% per year), free testosterone (1.3% per year)”)


1313. Haman SM, Metter EJ, Tobin JD, Blackman MR; Baltimore Longitudinal Study of Aging. Longitudinal effects of aging on serum total and free testosterone levels in healthy men. Baltimore Longitudinal Study of Aging. J Clin Endocrinol Metab. 2001 Feb;86(2):724-31 (The incidence of (overt) hypogonadal testosterone levels increased to about 20% of men over 60, 30% over 70 and 50% over 80 yr of age, and even greater percentages when free T index criteria were employed)


The speed of age-related decline of serum testosterone in men


Senescence in men is associated with a decline in metabolic clearance of testosterone


Senescence in men is associated with alterations of the circadian cycle of serum testosterone levels: reduced amplitude and desynchronization of its circadian rhythm


The age-related decline of serum testosterone starts in middle age in men


Senescence in men is associated with a loss of the circadian rhythm of serum testosterone


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Senescence in men is associated with an increased peripheral conversion of androgens into estrogens: the increased estrogen level in aging males may inhibit the androgen production


1324. Drafta D, Schindler AE, Stroe E, Neacsu E. Age-related changes of plasma steroids in normal adult males. J Steroid Biochem. 1982 Dec;17(6):683-7. (“The age related changes of plasma steroids in elderly men, were suggestive of decreased testicular function with increased peripheral conversion of androgens into estrogens. ... The negative correlation between estrone and 17-OH-P (precursor of testosterone) found in elderly men, suggested that increased estrogen level in aging males may be considered able to inhibit the testicular androgen production”)

Senescence in men is associated with a reduced sensitivity of the testosterone-producing Leydig cells to LH


Senescence is associated with a decline of the progesterone-adrenal axis in men

Reductions of progesterone levels with senescence in men


The progesterone increase after HCG stimulation disappears in elderly men


Functional decline with aging

Decline in functional capacity (vital capacity, nerve conduction velocity, cardiac index, renal blood flow, maximal breathing capacity, maximal work rate) : starts from age 30 on

1330. Backer GT and Martin GR. Molecular and biologic factors in aging: The origin, causes and prevention. Geriatric Medicine, 3rd ed., Springer, NY, 1997, p. 4 (no decline in personality , but decline in nerve condition, cardiac index, renal blood flow, maximal breathing capacity, maximal work rate)

Decrease in handgrip strength


Functional decline of the senses: from age 30 years on


Progressive appearance and increase in severity of physical aging signs with age

Hair grayness: start appearing from age 25 on


Wrinkles” start appearing from age 25

Wrinkles start appearing from age 25 and Pigment spots: after age 40


Sagging skin (after age 30)


Sagging skin increases with age and skin elasticity decreases with age: after age 30

1339. Ezure T, Hosoi J, Amano S, Tsuchiya T. Sagging of the cheek is related to skin elasticity, fat mass and mimetic muscle function. Skin Res Technol. 2009 Aug;15(3):299-305. (108 healthy Japanese female volunteers, aged 20-60 years. Each score was significantly correlated positively with age (20-60 years). In middle-aged volunteers, the sagging scores in all three areas of the cheek were significantly and negatively associated with skin elasticity.)

Skin elasticity decreases with age: increases from age 30 on


Skeletal muscle mass: declines from age 25-30 (third decade) on


Waist circumference: increases from age 25 on


Body fat: increases from age 25 on


Endocrine deficits after posttraumatic brain syndrome

Hypopituitarism in adults after traumatic brain injury

Research Institute, Harbor-UCLA Medical Center, Torrance, California Division of Neurosurgery, UCLA School of Medicine


Growth hormone deficiency after TBI


GH, ACTH deficiencies after TBI


GH, vasopressin and sexual hormone deficiencies after TBI


Research Institute, Harbor-UCLA Medical Center, Torrance, California Division of Neurosurgery, UCLA School of Medicine


**GH, TSH, thyroid, ACTH and cortisol deficiencies after TBI**


1371. Steven A. Lieberman Prevalence of Neuroendocrine Dysfunction in Patients Recovering from Traumatic Brain Injury1 J Clinical Endocrinology & Metabolism 2001 Vol. 86, No. 6 2752-2756

**Vasopressin, adrenal and thyroid deficiencies after TBI**


**Adrenal deficiency after TBI**


**Thyroid deficiencies after TBI**


**Hypogonadism, low testosterone/low female hormones**

1377. Agha A, Thompson CJ. High Risk of Hypogonadism After Traumatic Brain Injury: Clinical Implications Pituitary 8, Numbers 3-4: 245-249


**Physical aging signs associated with higher risks of disease and premature death**

**Higher risk of obesity in people with premature gray hair**


**Higher risk of arterial hypertension and atherosclerosis (thicker carotid artery intima media) in people with premature gray hair**

Higher risk of hypercholesterolemia and arterial hypertension in men with male pattern baldness

Higher risk of coronary heart disease in men with male pattern baldness

Higher risk of coronary heart disease and mortality in men with male pattern baldness

Higher coronary heart disease risk and higher all-cause mortality in men with male pattern baldness

Higher mortality from diabetes mellitus and heart disease in men with male pattern baldness and women with female pattern baldness

Higher risk of mortality in men with male pattern baldness

Higher risk of colon cancer in men with male pattern baldness
1396. Keum N, Cao Y, Lee DH, Park SM, Rosner B, Fuchs CS, Wu K, Giovannucci EL. Male pattern baldness and risk of colorectal neoplasia. Br J Cancer. 2016 Jan 12;114(1):110-7. (Significantly increased risks associated with frontal-only baldness and frontal-plus-mild-vertex baldness relative to no baldness were observed for colon cancer with respective HR being 1.29 (95% CI, 1.03-1.62) and 1.31 (95% CI, 1.01-1.70).

Higher risk of prostate cancer in men with male pattern baldness

Much higher risks of metabolic syndrome and atherosclerotic plaques in men with male pattern baldness and women with female pattern baldness

Higher risk of dyslipidemia in women with female pattern baldness

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Higher risk of coronary heart disease in women with female pattern baldness


Higher risk of decreased renal function in people with wrinkles

1402. Park BH, Lee S, Park JW, Kim KA, Kim HU, Lee JH, Koh DH, Youm JH, Yoo N, Park SK, Kwon KS. Facial wrinkles as a predictor of decreased renal function. Nephrology (Carlton). 2008 Dec;13(6):522-7. (lower eGFRs and higher LPO levels were found in those with severe facial wrinkles)

Anti-aging medicine and other preventive interventions: treating to better age and prevent disease


Efficacy of growth hormone therapy to attenuate aging and age-related diseases

GH therapy improves body composition in adults

Lean body mass: the improvement with GH treatment


1406. Bengtsson BA, Eden S, Lonn L, Kvist H, Stokland A, Lindstedt G, Bosaeus I, Toll J, Spjostrom L, Isaksson OG. Treatment of adults with growth hormone (GH) deficiency with recombinant human GH. J Clin Endocrinol Metab. 1993 Feb;76(2):309-17 (Subcutaneous AT decreased by an average of 13%, whereas visceral AT was reduced by 30%. Muscle volume increased by 2.5 kg (5%; P < 0.05). .. Total body water, body cell mass and extracellular fluid volume increased significantly by 1.6 and 3.0 kg, whereas body fat decreased by 6.1 kg)


Lean mass: the increase with GH treatment; fat mass: the reduction with GH treatment


Sarcopenia: the improvement with GH treatment


Physical appearance, body morphology improvement with GH treatment
GH therapy improves physical performance in adults

GH therapy: Improvement of exercise capacity and cardiac output

GH therapy: Improvement of cardiac output

GH therapy: No improvement of cardiac output
1425. Andreassen M, Faber J, Kjaer A, Petersen CL, Kristensen LØ. Cardiac function in growth hormone deficient patients before and after 1 year with replacement therapy: a magnetic resonance imaging study. Pituitary. 2011 Mar;14(1):1-10. (Sixteen patients (8 males and 8 females, mean age 49 years (range 18-75)) with severe GHD and 16 matched control subjects were included. year of GH replacement using physiological doses did not influence cardiac mass or function.)

GH therapy: Improvement of muscular strength
1426. Cuneo RC, Salomon F, Wiles CM, Hesp R, Sønksen PH. Growth hormone treatment in growth hormone-deficient adults. I. Effects on muscle mass and strength. J Appl Physiol (1985). 1991 Feb;70(2):688-94. (Strength of hip flexors (+1.25 +/- 0.27 vs. +0.25 +/- 0.12 z-scores; P = 0.004) and limb girdle muscles increased (P = 0.02) in the rGH group. ... the increase in strength of limb girdle muscles after rGH treatment suggests that adults with GH deficiency may have a proximal myopathy)
1427. Johannsson G, Grimbly G, Sunnerhagen KS, Bengtsson BA. Two years of growth hormone (GH) treatment increase isometric and isokinetic muscle strength in GH-deficient adults. J Clin Endocrinol Metab. 1997 Sep;82(9):2877-84. (The increase in muscle strength was more marked in younger patients and in patients with Plower initial muscle strength than predicted.)

GH therapy improves mental performance in adults

Memory loss: the improvement with GH treatment

GH therapy improves the mood and sexuality in adults

Lower quality of life and fatigue: the improvement with GH treatment
Spieghagen C, Schwahn C, Möller K, Friedrich N, Kohlmann T, Moock J, Koltowska-Häggström M, Nauck M, Buchfelder M, Wallaschekofski H. The benefit of long-term growth hormone (GH) replacement therapy in hypopituitary adults with GH deficiency: results of the German KIMS database. Growth Horm IGF Res. 2011 Feb;21(1):1-10. (long-term data (range: 4-10 years) of 440 consecutively documented patients (216 women and 224 men) with GHD, aged 20 to 49 years, enrolled in KIMS Germany The mean dose of GH over all years was 0.41 mg per day in women and 0.37 mg per day in men. IGF-I and IGF-I SDS levels (standard deviation score) increased significantly (p<0.001) during GH treatment. The QoL-AGHDA score decreased significantly (p<0.001), indicating long-lasting improvement in QoL. In total cholesterol, LDL-C and fasting blood glucose, no significant changes were found. Only six patients developed type 2 diabetes during follow-up. Females and males similarly increased significantly in BMI, WC and HC. During GH treatment, recurrences of pituitary or central nervous system tumours or further de novo neoplasia were reported in 6 or 11 patients, respectively.

The number of the most frequently reported GH treatment-associated adverse events was low


Atherosclerosis: the improvement with GH treatment


Arterial hypertension: the improvement with GH treatment


Heart failure and cardiac hypofunction: the improvement with GH treatment
Obesity and visceral adiposity: the improvement with GH treatment in adults


Insulin resistance, type 2 diabetes: the improvement with GH treatment in adults


1493. Toogood AA, Shalet SM. Growth hormone replacement therapy in the elderly with hypothalamic-pituitary disease: a dose-finding study. J Clin Endocrinol Metab. 1999 Jan;84(1):131-6 (fall in fat mass (P = 0.0003) and an increase in lean body mass (P = 0.0001). GH was well tolerated in this elderly group)


Osteoporosis: the improvement with long-term GH treatment


**Longevity: the association with GH and/or IGF-1 levels**


**Longevity: the association with higher IGF-1 levels**


1521. Ruiz-Torres A, Soares de Melo Kirzner M. Ageing and longevity are related to growth hormone/insulin-like growth factor-1 secretion. Gerontology. 2002 Nov-Dec;49(6):401-7

Mortality in GH deficient adults: no significant change with growth hormone therapy


Liver failure mortality: reduction with GH treatment

1526. Li N, Zhou L, Zhang B, Dong P, Lin W, Wang H, Xu R, Ding H. Recombinant human growth hormone increases albumin and prolongs survival in patients with chronic liver failure: a pilot open, randomized, and controlled clinical trial. Dig Liver Dis. 2008 Jul;40(7):554-9 (114 patients with chronic liver failure were randomly divided into 2 groups: 56 patients in the rhGH treatment group received 4.5IU of rhGH intramuscularly daily for 4 weeks, rest no treatment. The survival rate of the rhGH treatment and control-treatment groups after 2 weeks, 1 month, 3 months, and 6 months of treatment was 98.21% vs. 75.86%, 91.07% vs. 62.07%, 66.07% vs. 22.41%, and 55.36% vs. 13.79%, respectively)

Higher mortalities for childhood-onset deficient adults who only received growth hormone during childhood

1527. 10: Carel JC, Ecosse E, Landier F, Meguellati M, Kauvelidou F, Rey G, Deodati A, Ferroli BB, Cianfarani S. Association between growth hormone therapy and mortality, cancer and cardiovascular risk: systematic review and meta-analysis. Growth Horm IGF Res. 2014 Aug;24(4):105-11. (The overall all-cause SMR was 1.19 (95% CI 1.08-1.32, p<0.001). Malignancy and cardiovascular SMRs were not significantly increased. Both the overall cancer SIR 2.74 (95% CI 1.18-5.41), and RR for second neoplasms 1.99 (95% CI 1.28-3.08, p=0.002), were significantly increased... The results of this meta-analysis may raise concern on the long-term safety of GH treatment. However, several confounders and biases may affect the analysis. Independent, long-term, well-designed studies are needed to properly address the issue of GH therapy safety.) => mainly in patients treated during childhood and adolescence, higher mortality because bigger body and stopped GH in adulthood!!


No higher mortalities for childhood-onset deficient adults who only received growth hormone during childhood

1529. Mo D, Hardin DS, Erfurth EM, Melmed S. Adult mortality or morbidity is not increased in childhood-onset growth hormone deficient patients who received pediatric GH treatment: an analysis of the Hypopituitary Control and Complications Study (HypoCCS). Pituitary. 2014 Oct;17(5):477-85. (no increased risk of mortality or incidence of cancer, stroke, or MI in adult GH)

Growth hormone receptor deficiency not associated with increased mortality


Second part: Answer to critics

2309.