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Preconceived idea that aging is not or poorly evitable and reversible

Aging is not inevitable, nor irreversible

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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

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Thyroid treatment trials (therapeutic test): improved hypothyroid symptoms in patients with thyroid trests within the reference range, confirming the diagnosis of (initial) underactive thyroid function

Depression: Beneficial thyroid treatment of "euthyroid" depressive patients, preferably with T3 (triiodothyronine)

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Hypercholesterolemia: significant reduction with thyroid treatment in "euthyroid" hypercholesterolemic patients with auto-immune thyroid disease

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Thyroid nodules, goiter or enlargment: significant reduction with thyroid treatment in "euthyroid" patients

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

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Preconceived idea that thyroxine alone as treatment of hypothyroidism

Dogma on the use of thyroxine alone to treat hypothyroidism

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

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

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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

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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)

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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:

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

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

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

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

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

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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

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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

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

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T3 is much more potent than T4

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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

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99. Stahl F, Schnorr D, Pilz C, Dorner G. Dehydroepiandrosterone (DHEA) levels in patients with prostatic cancer, heart diseases and under surgery stress. Exp Clin Endocrinol. 1992;99(2):68-70 (critic: no estrogen levels, nor dietary factors checked)

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-stege 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)*

101. Zagars GK, Pollack A, von Eschenbach AC. Serum testosterone - a significant determinant of metastatic relapse for irradiated localized prostate cancer. Urology. 1997 Mar;49(3):327-34

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)

102. Huggins C, Hodges CV. Studies on prostatic cancer. I. The effect of castration, of estrogen and of androgen injection on serum phosphatases in metastatic carcinoma of the prostate. Am Ass Cancer Research 1941; 293-297". at http://cancerres.aacrjournals.org/content/1/4/293.full.pdf+html

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

103. Tymchuk CN, Barnard RJ, Ngo TH, Aronson WJ. Role of testosterone, estradiol, and insulin in diet- and exercise-induced reductions in serum-stimulated prostate cancer cell growth in vitro. Nutr Cancer. 2002;42(1):112-6

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;

104. Boyle P, Koechlin A, Bota M, d'Onofrio A, Zaridze DG, Perrin P, Fitzpatrick J, Burnett AL, Boniol M. Endogenous and exogenous testosterone and the risk of prostate cancer and increased prostate specific antigen (PSA): a meta-analysis. BJU Int. 2016 Jan 18. [Epub ahead of print]
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):378-87. (While data from large, prospective, randomized, controlled trials are absent, TRT in select prostate cancer patients is likely safe. In the end)
106. Warburton D, Hobaugh C, Wang G, Lin H, Wang R. Testosterone replacement therapy and the risk of prostate cancer. Asian J Androl. 2015 Nov-Dec;17(6):878-81; discussion 880.(The current literature does not report a statistically significant increase in the development or progression of prostate cancer in men receiving testosterone replacement for symptomatic hypogonadism, and the prostate saturation theory provides a model explaining the basis for these results)
107. Kühn CM, Strasser H, Romming A, Wullich 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.)
108. Kacker R, Hult M, San Francisco IF, Conners WP, Rojas PA, Dewolf WC,Morgentaler A. Can testosterone therapy be offered to men on active surveillance for prostate cancer? Preliminary results. Asian J Androl. 2016 Jan-Feb;18(1):16-20.
109. Isbarn H, Pinthus JH, Marks LS, Montorsi F, Morales A, Morgentaler A, Schulman C. Testosterone and prostate cancer: revisiting old paradigms. Eur Urol. 2009 Jul;56(1):48-56 (the current European Association of Urology guidelines state that in hypogonadal men who were successfully treated for prostate cancer, testosterone treatment can be considered after a prudent interval)

110. Rinnab L, Gust K, Hautmann RE, Küfer R. [Testosterone replacement therapy and prostate cancer. The current position 67 years after the Huggins myth] Urologe A. 2009 May;48(5):516-22 (physicians cannot really justify withholding TRT from symptomatic patients after they have been successful treated for prostate cancer)
111. Morgentaler A, Schulman C. Testosterone and prostate safety. Front Horm Res. 2009;37:197-203 (the available evidence strongly suggests that testosterone therapy is safe for the prostate)
112. Morgentaler A. Testosterone therapy in men with prostate cancer: scientific and ethical considerations. J Urol. 2009 Mar;181(3):972-9 (the safety of testosterone therapy in men with prostate cancer, the limited available evidence suggests that such treatment may not pose an undue risk of prostate cancer recurrence or progression)
113. Shabsigh R, Crawford ED, Nehra A, Slawin KM. Testosterone therapy in hypogonadal men and potential prostate cancer risk: a systematic review. Int J Impot Res. 2009 Jan-Feb;21(1):9-23 (Of studies that met inclusion criteria, none demonstrated that testosterone therapy for hypogonadism increased prostate cancer risk or increased Gleason grade of cancer detected in treated vs untreated men)
114. Morgentaler A. Guilt by association: a historical perspective on Huggins, testosterone therapy, and prostate cancer. J Sex Med. 2008 Aug;5(8):1834-40
115. Morgentaler A. Testosterone replacement therapy and prostate cancer. Urol Clin North Am. 2007 Nov;34(4):555-63
116. Raynaud JP. Prostate cancer risk in testosterone-treated men. J Steroid Biochem Mol Biol. 2006 Dec;102(1-5):261-6 (During the clinical development of a new testosterone patch in more than 200 primary or secondary hypogonadal patients, no prostate cancer was diagnosed)
117. 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 ("the cancer rate in TRT trials is only approximately 1%, similar to detection rates in screening programs .. little reason to withhold testosterone replacement therapy from men with favorable outcomes after definitive treatment for prostate cancer")
118. Morgentaler A. Testosterone and prostate cancer: an historical perspective on a modern myth. Eur Urol. 2006 Nov;50(5):935-9 ("there is not now-nor has there ever been-a scientific basis for the belief that testosterone causes prostate cancer to grow")
119. Dobs AS, Morgentaler A. Does testosterone therapy increase the risk of prostate cancer? Endocr Pract. 2008 Oct;14(7):904-11 ("No evidence of an associated relationship between exogenous testosterone therapy and prostate cancer has emerged from clinical trials or adverse event report")

Studies where low testosterone apparently increases the risk of prostate cancer

The urinary free testosterone decreases with aging, while the incidence of prostate cancer increases

120. Morer-Fargas F, Nowakowski H. Die Testosteronausscheidung im Harn bei Männlichen Indivuen. Acta Endocrinol. 1965; 49: 443-52
121. Data from the Surveillance, Epidemiology, and End Results (SEER) Program Staff. Section III: Incidence. In: Cancer statistics review 1973-1986. Bethesda, MD: NIH;1989;III.45

Low serum testosterone is associated with an increased prostate cancer risk

122. Stattin P, Lumme S, Tenkanen L, Alfthan H, Jellum E, Hallmans G, Thoresen S, Hakulinen T, Luostarinen T, Lehtinen M, Dillner J, Stenman UH, Hakama M. High levels of circulating testosterone are not associated with increased prostate cancer risk: a pooled prospective study. Int J Cancer. 2004 Jan 20;108(3):418-24
123. Chen C, Weiss NS, Stanczyk FZ, Lewis SK, DiTommaso D, Etzioni R, Barnett MJ, Goodman GE. Endogenous sex hormones & prostate cancer risk: a case-control study nested within the Carotene and Retinol Efficacy Trial. Cancer Epidemiol Biomarkers Prev. 2003;12(12):1410-6
124. Morgentaler A, Bruning CO 3rd, DeWolf WC. Occult prostate cancer in men with low serum testosterone levels. JAMA. 1996 Dec 18;276(23):1904-6. *(digital rectal examination and PSA levels are insensitive indicators of prostate cancer in men with low total or free testosterone levels)*

Low serum testosterone levels have been found in prostate cancer patients

125. Morote J, Planas J, Ramirez C, Gómez E, Raventós CX, Placer J, Catalán R, de Torres IM. Evaluation of the serum testosterone to prostate-specific antigen ratio as a predictor of prostate cancer risk. BJU Int. 2010 Feb 1;105(4):481-4
126. Mearini L, Costantini E, Zucchi A, Mearini E, Bini V, Cottini E, Porena M. Testosterone levels in benign prostatic hypertrophy and prostate cancer. Urol Int. 2008;80(2):134-40
127. Karamanolakis D, Lambou T, Bogdanos J, Milathianakis C, Sourla A, Lembessis P, Halapas A, Pissimissis N, Dessypris N, Petridou ET, Koutsilieris M. Serum testosterone: A potentially adjunct screening test for the assessment of the risk of prostate cancer among men with modestly elevated PSA values (> or =3.0 and <10.0 ng/ml). Anticancer Res. 2006 Jul-Aug;26(4B):3159-66.
128. Rivera P, Tagle R, Mir S, González R. Relationship between serum testosterone levels and prostatic cancer. Actas Urol Esp. 2003 Nov-Dec;27(10):788-92.

129. Zhonghua Yi Xue Za Zhi 1993; 73: 489-90 (mentioned in The natural prostate cure - Proger Mason 2000 ISBN 1-884820-61-1)
130. Kumar VL, Wadhwa SN, Kumar V, Farooq A. Androgen, estrogen, and progesterone receptor contents and serum hormone profiles in patients with benign hypertrophy and carcinoma of the prostate. J Surg Oncol. 1990 Jun;44(2):122-8
131. Revista Experimental Fisiology 1991; 47: 161-6 (mentioned in The natural prostate cure (Proger Mason 2000 ISBN 1-884820-61-1))
132. Revista Experimental Fisiology 1990; 46:63-8 (mentioned in The natural prostate cure (Proger Mason 2000 ISBN 1-884820-61-1)
133. Rannikko S, Adlercreutz H. Plasma estradiol, free testosterone, sex hormone binding globulin binding capacity, and prolactin in benign prostatic hyperplasia and prostatic cancer. Prostate. 1983;4(3):223-9
134. Meikle AW, Stanish WM. Familial prostatic cancer risk and low testosterone. J Clin Endocrinol Metab 1982 Jun;54(6):1104-8
135. Zumoff B, Levin J, Strain GW, Rosenfeld RS, O'Connor J, Freed SZ, Kream J, Whitmore WS, Fukushima DK, Hellman L. Abnormal levels of plasma hormones in men with prostate cancer: evidence toward a "two-disease" theory. Prostate. 1982;3(6):579-88 (Low testosterone in prostate cancer patients less than 65 years)
136. Vestsi Akademii Medicina Navuk USSR 1980; 3: 72-7 (mentioned in The natural prostate cure (Proger Mason 2000 ISBN 1-884820-61-1)°
137. Turkes AO, Turkes A, Read GF, Fahmy DR. A sensitive fluorometric enzyme immunoassay for testosterone in plasma and saliva [proceedings] J Endocrinol. 1979 Oct;83(1):31P
138. Progress in Clinical Biological Research 1975; 6: 143-58 (mentioned in The natural prostate cure - Proger Mason 2000 ISBN 1-884820-61-1))

Close to statistical significance lower testosterone levels in prostate cancer patients

139. Hulka BS, Hammond JE, DiFerdinando G, Mickey DD, Fried FA, Checkoway H, Stumpf WE, Beckman WC Jr, Clark TD. Serum hormone levels among patients with prostatic carcinoma or benign prostatic hyperplasia and clinic controls. Prostate. 1987;11(2):171-82
140. Gustafsson O, Norming U, Gustafsson S, Eneroth P, Astrom G, Nyman CR. Dihydrotestosterone and testosterone levels in men screened for prostate cancer:a study of a randomized population. Br J Urol. 1996 Mar;77(3):433-40
141. Nomura A, Heilbrun LK, Stemmermann GN, Judd HL. Prediagnostic serum hormones and the risk of prostate cancer. Cancer Res. 1988 Jun 15;48(12):3515-7

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

142. Meikle AW, Stanish WM. Familial prostatic cancer risk and low testosterone. J Clin Endocrinol Metab. 1982 Jun;54(6):1104-8

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

143. Wu AH, Whittemore AS, Kolonel LN, John EM, Gallagher RP, West DW, Hankin J, Teh CZ, Dreon DM, Paffenbarger RS Jr. Serum androgens and sex hormone-binding globulins in relation to lifestyle factors in older African-American, white, and Asian men in the United States and Canada. Cancer Epidemiol Biomarkers Prev. 1995 Oct-Nov;4(7):735-41

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

144. Morgentaler A, Bruning CO 3rd, DeWolf WC. Occult prostate cancer in men with low serum testosterone levels. JAMA. 1996 Dec 18;276(23):1904-6.

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

145. Wu AH, Whittemore AS, Kolonel LN, John EM, Gallagher RP, West DW, Hankin J, Teh CZ, Dreon DM, Paffenbarger RS Jr. Serum androgens and sex hormone-binding globulins in relation to lifestyle factors in older African-American, white, and Asian men in the United States and Canada. Cancer Epidemiol Biomarkers Prev. 1995 Oct-Nov;4(7):735-41 (*Asian-Americans had higher total and bioavailable testosterone compared to African-Americans and whites)*

Studies where a low serum dihydrotestosterone (DHT) was found in prostate cancer patients

146. Zumoff B, Levin J, Strain GW, Rosenfeld RS, O'Connor J, Freed SZ, Kream J, Whitmore WS, Fukushima DK, Hellman L. Abnormal levels of plasma hormones in men with prostate cancer: evidence toward a "two-disease" theory. Prostate. 1982;3(6):579-88 *(Low in prostate cancer patients less than 65 years)*

147. Signorello LB, Tzonou A, Mantzoros CS, Lipworth L, Lagiou P, Hsieh C, Stampfer M, Trichopoulos D. Serum steroids in relation to prostate cancer risk in a case-control study (Greece). Cancer Causes Control. 1997 Jul;8(4):632-6

A study where DHT is inversely, significantly, and strongly associated with the risk of prostate cancer

148. Signorello LB, Tzonou A, Mantzoros CS, Lipworth L, Lagiou P, Hsieh C, Stampfer M, Trichopoulos D. Serum steroids in relation to prostate cancer risk in a case-control study (Greece). Cancer Causes Control. 1997 Jul;8(4):632-6

Studies where close to statistical significance lower DHT levels were found in prostate cancer patients

149. Gustafsson O, Norming U, Gustafsson S, Eneroth P, Astrom G, Nyman CR. Dihydrotestosterone and testosterone levels in men screened for prostate cancer:a study of a randomized population. Br J Urol. 1996 Mar;77(3):433-40
150. Nomura A, Heilbrun LK, Stemmermann GN, Judd HL. Prediagnostic serum hormones and the risk of prostate cancer. Cancer Res. 1988 Jun 15;48(12):3515-7

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

151. Mohr BA, Feldman HA, Kalish LA, Longcope C, McKinlay JB. Are serum hormones associated with the risk of prostate cancer? Prospective results from the Massachusetts Male Aging Study. Urology. 2001 May;57(5):930-5.

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 locallyinvasive &/or metastatic

152. Pichon A, Neuzillet Y, Botto H, Raynaud JP, Radulescu C, Molinié V, Herve JM, Lebret T. Preoperative low serum testosterone is associated with high-grade prostate cancer and an increased Gleason score upgrading. Prostate Cancer Prostatic Dis. 2015 Dec;18(4):382-7.
153. Shiota M, Takeuchi A, Sugimoto M, Dejima T, Kashiwagi E, Kiyoshima K, Inokuchi J, Tatsugami K, Yokomizo A. Low Serum Testosterone But Not Obesity Predicts High Gleason Score at Biopsy Diagnosed as Prostate Cancer in Patients with Serum PSA Lower than 20 ng/ml. Anticancer Res. 2015 Nov;35(11):6137-45.
154. Kwon T, Jeong IG, You D, Park MC, Hong JH, Ahn H, Kim CS. 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)*
155. Lane BR, Stephenson AJ, Magi-Galluzzi C, Lakin MM, Klein EA. Low testosterone and risk of biochemical recurrence and poorly differentiated prostate cancer at radical prostatectomy. Urology. 2008 Dec;72(6):1240-5.
156. Imamoto T, Suzuki H, Yano M, Kawamura K, Kamiya N, Araki K, Komiya A, Naya Y, Shiraishi T, Ichikawa T. Does presence of prostate cancer affect serum testosterone levels in clinically localized prostate cancer patients? Prostate Cancer Prostatic Dis. 2009;12(1):78-82
157. Lackner JE, Maerk I, Koller A, Bieglmayer C, Marberger M, Kratzik C, Schatzl G. Serum inhibin--not a cause of low testosterone levels in hypogonadal prostate cancer? Urology. 2008 Nov;72(5):1121-4
158. Mearini L, Costantini E, Zucchi A, Mearini E, Bini V, Cottini E, Porena M. Testosterone levels in benign prostatic hypertrophy and prostate cancer. Urol Int. 2008;80(2):134-40
159. Sekine Y, Ito K, Yamamoto T, Nakazato H, Shibata Y, Hatori M, Suzuki K. Pretreatment total testosterone levels in patients with prostate cancer in the past two decades in Japan. Cancer Detect Prev. 2007;31(2):149-53
160. 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 see comment below in section 'Arguments contra testosterone therapies')*
161. San Francisco IF, Regan MM, Dewolf WC, Olumi AF. Low age adjusted free testosterone levels correlate with poorly differentiated prostate cancer. J Urol. 2006 Apr;175(4):1341-5
162. Teloken C, Da Ros CT, Caraver F, Weber FA, Cavalheiro AP, Graziottin TM.(editorial note *A Bohle).* Low serum testosterone levels are associated with positive surgical margins in radical retropubic prostatectomy: hypogonadism represents bad prognosis in prostate cancer. Int Braz J Urol. 2005 Nov-Dec;31(6):609
163. Teloken C, Da Ros CT, Caraver F, Weber FA, Cavalheiro AP, Graziottin TM. Low serum testosterone levels are associated with positive surgical margins in radical retropubic prostatectomy: hypogonadism represents bad prognosis in prostate cancer. J Urol. 2005 Dec;174(6):2178-80
164. Isom-Batz G, Bianco FJ Jr, Kattan MW, Mulhall JP, Lilja H, Eastham JA. Testosterone as a predictor of pathological stage in clinically localized prostate cancer. J Urol. 2005 Jun;173(6):1935-7

165. Imamoto T, Suzuki H, Fukasawa S, Shimbo M, Inahara M, Komiya A, Ueda T, Shiraishi T, Ichikawa T. Pretreatment serum testosterone level as a predictive factor of pathological stage in localized prostate cancer patients treated with radical prostatectomy. Eur Urol. 2005 Mar;47(3):308-12
166. Schatzl G, Madersbacher S, Haitel A, Gsur A, Preyer M, Haidinger G, Gassner C, Ochsner M, Marberger M. Associations of serum testosterone with microvessel density, androgen receptor density and androgen receptor gene polymorphism in prostate cancer. J Urol. 2003 Apr;169(4):1312-5
167. Schatzl G, Madersbacher S, Thurridl T, Waldmüller J, Kramer G, Haitel A, Marberger M. High-grade prostate cancer is associated with low serum testosterone levels. Prostate. 2001 Apr;47(1):52-8.
168. Hoffman MA, DeWolf WC, Morgentaler A. Is low serum free testosterone a marker for high grade prostate cancer? J Urol. 2000 Mar;163(3):824-7
169. Haapiainen R, Rannikko S, Alfthan O, Adlercreutz H. Pretreatment plasma levels of testosterone and sex hormone binding globulin binding capacity in relation to clinical staging and survival in prostatic cancer patients. Prostate. 1988;12(4):325-32

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

170. Schatzl G, Marberger M, Remzi M, Grosser P, Unterlechner J, Haidinger G, Zidek T, Preyer M, Micksche M, Gsur A. Polymorphism in ARE-I region of prostate-specific antigen gene associated with low serum testosterone level and high-grade prostate cancer. Urology. 2005 Jun;65(6):1141-5

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

171. Imamoto T, Suzuki H, Fukasawa S, Shimbo M, Inahara M, Komiya A, Ueda T, Shiraishi T, Ichikawa T. Pretreatment serum testosterone level as a predictive factor of pathological stage in localized prostate cancer patients treated with radical prostatectomy. Eur Urol. 2005 Mar;47(3):308-12

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)

172. Furuya Y, Nozaki T, Nagakawa O, Fuse H. Low serum testosterone level predicts worse response to endocrine therapy in Japanese patients with metastatic prostate cancer. Endocr J. 2002 Feb;49(1):85-90
173. 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

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

174. Titus MA, Schell MJ, Lih FB, Tomer KB, Mohler JL. Testosterone and dihydrotestosterone tissue levels in recurrent prostate cancer. Clin Cancer Res. 2005 Jul 1;11(13):4653-7. *(11-fold lower DHT level 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**

175. Mohler JL, Gregory CW, Ford OH 3rd, Kim D, Weaver CM, Petrusz P, Wilson EM, French FS. The androgen axis in recurrent prostate cancer. Clin Cancer Res. 2004 Jan 15;10(2):440-8

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

176. Ribeiro M, Ruff P, Falkson G. Low serum testosterone and a younger age predict for a poor outcome in metastatic prostate cancer. Am J Clin Oncol 1997 Dec;20(6):605-8
177. Iversen P, Rasmussen F, Christensen IJ. Serum testosterone as a prognostic factor in patients with advanced prostatic carcinoma. Scand J Urol Nephrol Suppl. 1994; 157: 41-7
178. Haapiainen R, Rannikko S, Alfthan O, Adlercreutz H. Pretreatment plasma levels of testosterone and sex hormone binding globulin binding capacity in relation to clinical staging and survival in prostatic cancer patients. Prostate. 1988;12(4):325-32
179. Ribeiro M, Ruff P, Falkson G. Low serum testosterone and a younger age predict for a poor outcome in metastatic prostate cancer. Am J Clin Oncol. 1997 Dec;20(6):605-8

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

180. Taira AV, Merrick GS, Galbreath RW, Butler WM, Wallner KE, Allen ZA, Lief JH, Adamovich E. Pretreatment serum testosterone and androgen deprivation: effect on disease recurrence and overall survival in prostate cancer patients treated with brachytherapy. Int J Radiat Oncol Biol Phys. 2009 Jul 15;74(4):1143-9. *(Prostate cancer patients with baseline low testosterone who also were treated with androgen deprivation therapy had a trend toward decreased overall survival)*

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)

181. Leibowitz RL, Dorff TB, Tucker S, Symanowski J, Vogelzang NJ. Testosterone replacement in prostate cancer survivors with hypogonadal symptoms. 6. BJU Int. 2009 Nov 5. [Epub ahead of print]
182. Conti PD, Atallah AN, Arruda H, Soares BG, El Dib RP, Wilt TJ. Intermittent versus continuous androgen suppression for prostatic cancer. Cochrane Database Syst Rev. 2007 Oct 17;(4):

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

183. Ortega E, Ruiz E, Mendoza MC, Martin-Andres A, Osorio C. Plasma steroid and protein hormone concentrations in patients with benign prostatic hypertrophy and in normal men. Experientia. 1979 Jun 15;35(6):844-5

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

184. Wright F, Poizat, Bongini M,Bozzolan F Doukani A, Mauvais-Jarvis P. Decreased urinary 5-alpha-androstanediol glucuronide excretion in patients with benign prostatic hyperplasia. J Clin Endocrinol Metab. 1985; 60 (2) 294-8

Men with chronic prostatitis have often low testosterone

185. Yunda IF, Imshinetskaya LP. Testosterone excretion in chronic prostatis. 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 correlative dependence on severity of clinical symptoms, duration of disease and form of chronic prostatis.")*

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

187. Feyel-Cabanes T, Secchi J, Robel P, Baulieu EE. Combined effects of testosterone and estradiol on rat ventral prostate in organ culture. Cancer Res. 1978 Nov;38(11 Pt 2):4126-34.
188. Feyel-Cabanes T, Robel P, Baulieu EE. Combined effects of testosterone and estradiol on the ventral lobe of the rat postate in organ culture. C R Acad Sci Hebd Seances Acad Sci D. 1977 Oct 31;285(11):1119-22

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

189. Morales A, Connolly JG, Bruce AW. Androgen therapy in advanced carcinoma of the prostate. Can Med Assoc J. 1971;105(1):71-2
190. Prout GR Jr, Brewer WR. Response of men with advanced prostatic carcinoma to exogenous administration of testosterone. Cancer. 1967 Nov;20(11):1871-8

Studies where testosterone/androgen treatment of patients with advanced prostate cancer increased their quality of life wit no increase in recurrence

191. Kaplan AL, Hu JC, Morgentaler A, Mulhall JP, Schulman CC, Montorsi F. Testosterone therapy in men with prostate cancer. Eur Urol. 2015 Dec 21. [Epub ahead of print]
192. Baillargeon J, Kuo YF, Fang X, Shahinian VB. Long-term Exposure to Testosterone Therapy and the Risk of High Grade Prostate Cancer. J Urol. 2015 Dec;194(6):1612-6.

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

193. Joly-Pharaboz MO, Soave MC, Nicolas B, Mebarki F, Renaud M, Foury O, Morel Y, Andre JG. Androgens inhibit the proliferation of a variant of the human prostate cancer cell line LNCaP. J Steroid Biochem Mol Biol 1995 Oct;55(1):67-76
194. Wolf DA, Schulz P, Fittler F. Synthetic androgens suppress the transformed phenotype in human prostate carcinoma cell line LNCaP. Br J Cancer. 1991 Jul; 64 (1): 47-53

195. Andrews P, Krygier S, Djakiew D. Dihydrotestosterone (DHT) modulates the ability of NSAIDs to induce apoptosis of prostate cancer cells. Cancer Chemother Pharmacol. 2002 Mar;49(3):179-86

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

196. Flamm J, Kiesswetter H, Englisch M. An urodynamic study of patients with benign prostatic hypertrophy treated conservatively with phytotherapy or testosterone. Wien Klin Wochenschr 1979 Sep 28;91(18):622-7
197. Kearns WM. Testosterone in the treatment of testicular deficiency and prostatic enlargement. Wisconsin Med J. 1941; 40:927 *(testosterone proprionate 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
199. Trasoff A. The treatment of benign prostatic hypertrophy with testosterone propionate. J Lab Clin Med. 1940; 25: 377
200. Markham MJ. The clinical use of peroral methyltestosterone in benign prostatic hypertrophy. Urol Cutan Rev. 1942; 46: 225
201. Markham MJ. The clinical use of testosterone propionate in benign prostatic hypertrophy. Urol Cutan Rev. 1941; 45: 35
202. Laqueur E. Behandlung der Prostathypertropie mit männlichen Hormone (Hombreol) une experimentell Begründung dieser Therapie. Schweiz Med Wochenschr. 1934; 64: 1116 South Med J, 1939, 32: 154

Study where testosterone treatment reduces prostate stromal hyperplasia and prostatic complaints (prostatism)

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

203. de Lignieres B. Transdermal dihydrotestosterone treatment of 'andropause. Ann Med 1993 Jun;25(3):235-41
204. Swerdloff RS, Wang C. Dihydrotestosterone: a rationale for its use as a non-aromatizable androgen replacement therapeutic agent. Baillieres Clin Endocrinol Metab. 1998 Oct;12(3):501-6
205. Sitruk-Ware R. Contraception, 1989, 39: 1-191

Animal studies:

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

206. Jennbacken K, Gustavsson H, Tesan T, Horn M, Vallbo C, Welén K, Damber JE. The prostatic environment suppresses growth of androgen-independent prostate cancer xenografts: an effect influenced by testosterone. Prostate. 2009 Aug 1;69(11):1164-75. *(Castration of mice increased tumor growth of prostate cancer implanted in the prostate.)*

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

207. Sato N, Watabe Y, Suzuki H, Shimazaki J. Progression of androgen-sensitive mouse tumor (Shionogi carcinoma 115) to androgen-insensitive tumor after long-term removal of testosterone. Jpn J Cancer Res. 1993 Dec;84(12):1300-8

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

208. Akaza H, Tsukamoto S, Morita T, Yamauchi A, Onozawa M, Shimazui T, Ideyama Y, Shirai T. Promoting effects of antiandrogenic agents on rat ventral prostate carcinogenesis induced by 3,2'-dimethyl-4-aminobiphenyl (DMAB). Prostate Cancer Prostatic Dis. 2000 Aug;3(2):115-9
209. Thompson IM, Goodman PJ, Tangen CM, Lucia MS, Miller GJ, Ford LG, Lieber MM, Cespedes RD, Atkins JN, Lippman SM, Carlin SM, Ryan A, Szczepanek CM, Crowley JJ, Coltman CA Jr. The influence of finasteride on the development of prostate cancer. N Engl J Med. 2003;349(3):215-24

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.

210. Bondarenko LA, Breslavskii AS, Vartapetov BA, Gladkova AI. Secretion of testicular androgens under conditions of chronic experimental inflammation of the prostate gland. Probl Endokrinol (Mosk). 1977 Jul-Aug;23(4):111-5

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

211. Feyel-Cabanes T, Secchi J, Robel P, Baulieu EE. Combined effects of testosterone and estradiol on rat ventral prostate in organ culture. Cancer Res. 1978 Nov;38(11 Pt 2):4126-34.

A study where testosterone treatment reduces the proliferation of mouse prostate cancer cells in vitro

212. Suzuki H, Nihei N, Sato N, Ichikawa T, Mizokami A, Shimazaki J. Inhibition of growth and increase of acid phosphatase by testosterone on androgen-independent murine prostatic cancer cells transfected with androgen receptor cDNA. Prostate. 1994 Dec;25(6):310-9

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

213. Ricciardelli C, Horsfall DJ, Sykes PJ, Marshall VR, Tilley WD. Effects of oestradiol-17 beta and 5 alpha-dihydrotestosterone on guinea- pig prostate smooth muscle cell proliferation and steroid receptor expression in vitro. J Endocrinol. 1994 Mar;140(3):373-83

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

214. 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

215. Burrows H. Nature (London). 1936, 138: 164

A study that shows that testosterone treatment of castrated mice can inhibit the progression of androgen-independent prostate cancer in vivo

216. Jennbacken K, Gustavsson H, Tesan T, Horn M, Vallbo C, Welén K, Damber JE. The prostatic environment suppresses growth of androgen-independent prostate cancer xenografts: an effect influenced by testosterone. Prostate. 2009 Aug 1;69(11):1164-75. *(Castration of the mice increased tumor growth of prostate cancer implanted in the prostate. This effect was reversed by testosterone treatment)*

A study where testosterone treatment of certain species of mice can inhibit prostate cancer growth

217. Umekita Y, Hiipakka RA, Kokontis JM, Liao S. Human prostate tumor growth in athymic mice: inhibition by androgens and stimulation by finasteride. Proc Natl Acad Sci U S A 1996 Oct 15;93(21):11802-7

Studies where dihydrotestosterone treatment of certain species of rats can inhibit prostate cancer growth

218. Pollard M. Dihydrotestosterone prevents spontaneous adenocarcinomas in the prostate-seminal vesicle in aging L-W rats. Prostate 1998 Aug 1;36(3):168-71
219. Pollard M, Luckert PH, Snyder D.Prevention and treatment of experimental prostate cancer in Lobund-Wistar rats. I. Effects of estradiol, dihydrotestosterone, and castration. Prostate 1989;15(2):95-103

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

220. 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
221. Ripple MO, Hagopian K, Oberley TD, Schatten H, Weindruch R. Androgen-induced oxidative stress in human LNCaP prostate cancer cells is associated with multiple mitochondrial modifications. Antioxid Redox Signal. 1999 Spring;1(1):71-81
222. Ripple MO, Henry WF, Rago RP, Wilding G. Prooxidant-antioxidant shift induced by androgen treatment of human prostate carcinoma cells. J Natl Cancer Inst. 1997 Jan 1;89(1):40-8 *("Physiologic levels of androgens are capable of increasing oxidative stress in androgen-responsive LNCaP prostate carcinoma cells")*

A study where dihydrotestosterone treatment stimulates apoptosis of prostate cancer cells

223. Bruckheimer EM, Kyprianou N. Dihydrotestosterone enhances transforming growth factor-beta-induced apoptosis in hormone-sensitive prostate cancer cells. Endocrinology. 2001 Jun;142(6):2419-26

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 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")
228. Wirth MP, Hakenberg OW Testosterone and the prostate. Urologe A 2000 Sep;39(5):418-20
229. Rolf C, Nieschlag E. Potential adverse effects of long-term testosterone therapy. Baillieres Clin Endocrinol Metab. 1998 Oct;12(3):521-34.
230. Prehn RT. On the prevention and therapy of prostate cancer by androgen administration. Cancer Res. 1999 Sep 1;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. 2009 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, Traish 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

235. Endogenous Hormones and Prostate Cancer Collaborative Group, Roddam AW, Allen NE, Appleby P, Key TJ. Endogenous sex hormones and prostate cancer: a collaborative analysis of 18 prospective studies. J Natl Cancer Inst. 2008 Feb 6;100(3):170-83
236. Hong SK, Han BK, Jeong JS, Jeong SJ, Moon KH, Byun SS, Lee SE. Serum measurements of testosterone, insulin-like growth factor 1, and insulin-like growth factor binding protein-3 in the diagnosis of prostate cancer among Korean men. Asian J Androl. 2008 Mar;10(2):207-13
237. Mohr BA, Feldman HA, Kalish LA, Longcope C, McKinlay JB. Are serum hormones associated with the risk of prostate cancer? Prospective results from the Massachusetts Male Aging Study. Urology. 2001 May;57(5):930-5.
238. Schatzl G, Reiter WJ, Thürridl T, Waldmüller J, Roden M, Söregi S, Madersbacher S. Endocrine patterns in patients with benign and malignant prostatic diseases. Prostate. 2000 Aug 1;44(3):219-24.

239. Heikkila R, Aho K, Heliovaara M, Hakama M, Marniemi J, Reunanen A, Knekt P. Serum testosterone and sex hormone-binding globulin concentrations and the risk of prostate carcinoma: a longitudinal study. Cancer. 1999 Jul 15;86(2):312-5
240. Dorgan JF, Albanes D, Virtamo J, Heinonen OP, Chandler DW, Galmarini M, McShane LM, Barrett MJ, Tangrea J, Taylor PR. Relationships of serum androgens and estrogens to prostate cancer risk: results from a prospective study in Finland. Cancer Epidemiol Biomarkers Prev. 1998 Dec;7(12):1069-74.
241. Vatten LJ, Ursin G, Ross RK, Stanczyk FZ, Lobo RA, Harvei S, Jellum E. Androgens in serum and the risk of prostate cancer: a nested case-control study from the Janus serum bank in Norway. Cancer Epidemiol Biomarkers Prev 1997 Nov;6(11):967-9
242. Nomura AM, Stemmermann GN, Chyou PH, Henderson BE, Stanczyk FZ. Serum androgens and prostate cancer. Cancer Epidemiol Biomarkers Prev 1996 Aug;5(8):621-5
243. Nomura A, Heilbrun LK, Stemmermann GN, Judd HL. Prediagnostic serum hormones and the risk of prostate cancer. Cancer Res. 1988 Jun 15;48(12):3515-7.
244. Carter HB, Pearson JD, Metter EJ, Chan DW, Andres R, Fozard JL, Rosner W, Walsh PC. Longitudinal evaluation of serum androgen levels in men with and without prostate cancer. Prostate. 1995 Jul;27(1):25-31
245. Carter HB, Pearson JD, Metter EJ, Brant LJ, Chan DW, Andres R, Fozard JL, Walsh PC. Longitudinal evaluation of prostate-specific antigen levels in men with and without prostate disease. JAMA. 1992 Apr 22-29;267(16):2215-20.
246. Wright F, Poizat R, Bongini M, Bozzolan F, Doukani A, Mauvais-Jarvis P. Decreased urinary 5-alpha-androstanediol glucuronide excretion in patients with benign prostatic hyperplasia. J Clin Endocrinol Metab. 1985; 60 (2) 294-8
247. Habib FK, Lee IR, Stitch SR, Smith PH. Androgen levels in the plasma and prostatic tissues of patients with benign hypertrophy and carcinoma of the prostate. J Endocrinol 1976 OCT;71(1):99-107

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

248. Armstrong AJ, Halabi S, de Wit R, Tannock IF, Eisenberger M. The relationship of body mass index and serum testosterone with disease outcomes in men with castration-resistant metastatic prostate cancer. Prostate Cancer Prostatic Dis. 2009;12(1):88-93

Studies with no correlation between serum testosterone and serum PSA

249. Monath JR, McCullough DL, Hart LJ, Jarow JP. Physiologic variations of serum testosterone within the normal range do not affect serum prostate-specific antigen. Urology 1995 Jul;46(1):58-61
250. Monda JM, Myers RP, Bostwick DG, Oesterling JE. The correlation between serum prostate-specific antigen and prostate cancer is not influenced by the serum testosterone concentration. Urology 1995 Jul;46(1):62-4
251. Schatzl G, Reiter WJ, Thurridl T, Waldmuller J, Roden M, Soregi S, Madersbacher S. Endocrine patterns in patients with benign and malignant prostatic diseases. Prostate 2000;44(3):219-24
252. Vijayakumar S, Quadri SF, Dong L, Ignacio L, Kathuria IN, Sutton H, Halpern H. Results of a study to correlate serum prostate specific antigen and reproductive hormone levels in patients with localized prostate cancer. J Natl Med Assoc 1995 Nov;87(11):813-9

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)

253. Morote J, Ramirez C, Gómez E, Planas J, Raventós CX, de Torres IM, Catalán R. The relationship between total and free serum testosterone and the risk of prostate cancer and tumour aggressiveness. BJU Int. 2009 Aug;104(4):486-9. *("Prostate cancer risk and tumour aggressiveness are not related to serum levels of total and free testosterone")*
254. Mikkola AK, Aro JL, Rannikko SA, Salo JO. Pretreatment plasma testosterone and estradiol levels in patients with locally advanced or metastasized prostatic cancer. FINNPROSTATE Group. Prostate. 1999 May 15;39(3):175-81

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

255. Monda JM, Myers RP, Bostwick DG, Oesterling JE. The correlation between serum prostate-specific antigen and prostate cancer is not influenced by the serum testosterone concentration. Urology. 1995 Jul;46(1):62-4

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

256. Young HH 2nd, Kent JR. Plasma testosterone levels in patients with prostatic carcinoma before and after treatment. J Urol. 1968 Jun;99(6):788-92

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

257. Lagiou P, Mantzoros CS, Tzonou A, Signorello LB, Lipworth L, Trichopoulos D. Serum steroids in relation to benign prostatic hyperplasia. Oncology. 1997 Nov-Dec;54(6):497-501

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 localised 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

261. Morris MJ, Huang D, Kelly WK, Slovin SF, Stephenson RD, Eicher C, Delacruz A, Curley T, Schwartz LH, Scher HI. Phase 1 trial of high-dose exogenous testosterone in patients with castration-resistant metastatic prostate cancer. Eur Urol. 2009 Aug;56(2):237-44 *(n = 16; "patients with castration-resistant metastatic prostate cancer can be safely treated in clinical trials using high-dose exogenous testosterone. Patients did not, on average, achieve sustained supraphysiologic serum testosterone levels")*
262. Szmulewitz R, Mohile S, Posadas E, Kunnavakkam R, Karrison T, Manchen E, Stadler WM. A randomized phase 1 study of testosterone replacement for patients with low-risk castration-resistant prostate cancer. Eur Urol. 2009 Jul;56(1):97-103 *(n = 15; in men with early progressive castration-resistant prostate cancer transdermal testosterone treatment "is a feasible and reasonably well-tolerated therapy for men")*
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")
265. Brawer MK. Testosterone replacement therapy for a man with prostate cancer. Rev Urol. 2004;6 Suppl 6:S35-7..
266. Morales A, Black A. Testosterone deficiency syndrome and prostate cancer: illustrative annotations for a debate. Can Urol Assoc J. 2008 Feb;2(1):52-4.
267. Mathew P. Prolonged control of progressive castration-resistant metastatic prostate cancer with testosterone replacement therapy: the case for a prospective trial. Ann Oncol. 2008 Feb;19(2):395-6.

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

268. Prout GRJ, Brewer WR. Response of men with advanced prostatic carcinoma to exogenous administration of testosterone. Cancer (Phila.). 1967;*20:*1871-8
269. Trunnell JD, Duffy BJ Jr. The influence of certain steroids on the behavior of human prostate cancer. Trans. NY Acad Sci. 1950;II:12:238-41
270. Brendler H, Lowry O, Brock M. Further investigation of hormonal relationships. Arch Surg. 1950,61:433-40
271. Pearson OH. Discussion of Dr. Huggins' paper: "Control of cancers of man by endocrinological methods." Cancer Res. 1957:17:473-9

272. Morales A, Connolly J, Burr R, Bruce A. The use of radioactive phosphorus to treat bone pain in metastatic carcinoma of the prostate. Can Med Assoc J. 1970;103: 372-3

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

273. Rhoden 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)*
274. Shibasaki T, Sasagawa I, Suzuki Y, Yazawa H, Ichiyanagi O, Matsuki S, Miura M, Nakada T. Effect of testosterone replacement therapy on serum PSA in patients with Klinefelter syndrome. Arch Androl. 2001 Nov-Dec;47(3):173-6
275. Cooper CS, Perry PJ, Sparks AE, MacIndoe JH, Yates WR, Williams RD. Effect of exogenous testosterone on prostate volume, serum and semen prostate specific antigen levels in healthy young men. J Urol. 1998 Feb;159(2):441-3
276. Cooper CS, MacIndoe JH, Perry PJ, Yates WR, Williams RD. The effect of exogenous testosterone on total and free prostate specific antigen levels in healthy young men. J Urol. 1996 Aug;156(2 Pt 1):438-41
277. Behre HM, Bohmeyer J, Nieschlag E. Prostate volume in testosterone-treated and untreated hypogonadal men in comparison to age-matched normal controls. Clin Endocrinol (Oxf). 1994 Mar;40(3):341-9
278. Douglas TH, Connelly RR, McLeod DG, Erickson SJ, Barren R 3rd, Murphy GP. Effect of exogenous testosterone replacement on prostate-specific antigen and prostate-specific membrane antigen levels in hypogonadal men. J Surg Oncol. 1995 Aug;59(4):246-50
279. Sih R, Morley JE, Kaiser FE, Perry HM 3rd, Patrick P, Ross C. Testosterone replacement in older hypogonadal men: a 12-month randomized controlled trial. J Clin Endocrinol Metab. 1997 Jun;82(6):1661-7
280. Hajjar RR, Kaiser FE, Morley JE. Outcomes of long-term testosterone replacement in older hypogonadal males: a retrospective analysis. J Clin Endocrinol Metab. 1997 Nov;82(11):3793-6
281. Monath JR, McCullough DL, Hart LJ, Jarow JP. Physiologic variations of serum testosterone within the normal range do not affect serum prostate-specific antigen. Urology. 1995 Jul;46(1):58-61

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

282. Kunelius P, Lukkarinen O, Hannuksela ML, Itkonen O, Tapanainen JS. The effects of transdermal dihydrotestosterone in the aging male: a prospective, randomized, double blind study. J Clin Endocrinol Metab. 2002 Apr;87(4):1467-72

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

283. Behre HM, Bohmeyer J, Nieschlag E. Prostate volume in testosterone-treated and untreated hypogonadal men in comparison to age-matched normal controls. Clin Endocrinol (Oxf). 1994 Mar;40(3):341-9.
284. Behre HM, Nieschlag E. Testosterone buciclate (20 Aet-1) in hypogonadal men: pharmacokinetics and pharmacodynamics of the new long-acting androgen ester. J Clin Endocrinol Metab. 1992 Nov;75(5):1204-10
285. Guay AT, Perez JB, Fitaihi WA, Vereb M. Testosterone treatment in hypogonadal men: prostate-specific antigen level and risk of prostate cancer. Endocr Pract. 2000 Mar-Apr;6(2):132-8
286. McClellan KJ, Goa KL. Transdermal testosterone. Drugs 1998 Feb;55(2):253-8; discussion 259
287. Arver S, Dobs AS, Meikle AW, Caramelli KE, Rajaram L, Sanders SW, Mazer NA. Long-term efficacy and safety of a permeation-enhanced testosterone transdermal system in hypogonadal men. Clin Endocrinol (Oxf). 1997 Dec;47(6):727-37
288. Tenover JS. Effects of testosterone supplementation in the aging male. J Clin Endocrinol Metab. 1992 Oct;75(4):1092-8

Testosterone treatment does not increase the incidence of prostate disease

289. Hartnell J, 72nd Endocrine Soc. Meeting, 1990, A 428

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**

290. Lesser MA, Vose SN, Dixey GM. Effect of testosterone propionate on the prostate gland of patients over 45. J Clin Endocrinol Metab. 1955 Mar;15(3):297-300

Studies where DHT treatment had no effect on the prostate volume

291. Kunelius P, Lukkarinen O, Hannuksela ML, Itkonen O, Tapanainen JS. The effects of transdermal dihydrotestosterone in the aging male: a prospective, randomized, double blind study. J Clin Endocrinol Metab. 2002 Apr;87(4):1467-72.

292. Ly LP, Jimenez M, Zhuang TN, Celermajer DS, Conway AJ, Handelsman DJ. A double-blind, placebo-controlled, randomized clinical trial of transdermal dihydrotestosterone gel on muscular strength, mobility, and quality of life in older men with partial androgen deficiency. J Clin Endocrinol Metab. 2001 Sep;86(9):4078-88

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

293. Wang H, Wan YX, Zhang QK. Significance and expression of insulin-like growth factor 1 and IGF binding protein 3 in serum of patients with lung cancer. AiZheng. 2004 Jun;23(6):710-4

Higher IGF-1 levels in gastric cancer

294. Franciosi CM, Piacentini MG, Conti M, Romano F, Musco F, Caprotti R, Rovelli F, Uggeri F. IGF-1 and IGF-1BP3 in gastric adenocarcinoma. Preliminary study. Hepatogastroenterology. 2003 Jan-Feb;50(49):297-300

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

295. Bruning PF, Van Doorn J, Bonfrèr JM, Van Noord PA, Korse CM, Linders TC, Hart AA. Insulin-like growth-factor-binding protein 3 is decreased in early-stage operable pre-menopausal breast cancer. Int J Cancer. 1995 Jul 28;62(3):266-70 *(The IGF-I/IGFBP-3 ratio was a significant breast-cancer risk factor)*

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 ($p \leq 0.376$) for total IGF-I and 6.31 ($p \leq 0.047$) for free IGF-I. A high ratio of IGF-I to IGFBP-3 was also associated with breast cancer ($p < 0.05$))*

297. Hankinson SE, Willett WC, Colditz GA, Hunter DJ, Michaud DS, Deroo B, Rosner B Speizer FE, Pollak M. Circulating concentrations of insulin-like growth factor-I and risk of breast cancer. Lancet 1998 May 9;351(9113):1393-6 Int J Cancer 1998 Jun 10;76(6):787-90 *(A positive relation between circulating IGF-I concentration and risk of breast cancer was found among premenopausal but not postmenopausal women)*

298. Bohlke 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

300. Ron E, Gridley G, Hrubec Z, Page W, Arora S, Fraumeni JF Jr. Acromegaly and gastrointestinal cancer. Cancer. 1991 Oct 15;68(8):1673-7. National Cancer Institute, Bethesda, Maryland

301. Ma J, Pollak MN, et al. Prospecftive study of colorectal cancer risk in men and plasma levels of IGF-1 and IGF-BP-3. J Natl Cancer Inst. 1999; 91: 620-625

High levels in prostate cancer

302. Peng L, Tang S, Xie J, Luo T, Dai B. Quantitative analysis of IGF-1 and its application in the diagnosis of prostate cancer. Hua Xi Yi Ke Da Xue Xue Bao. 2002 Jan;33(1):137

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 fators - see further)*

303. Peng L, Tang S, Xie J, Luo T, Dai B. Quantitative analysis of IGF-1 and its application in the diagnosis of prostate cancer. Hua Xi Yi Ke Da Xue Xue Bao. 2002 Jan;33(1):137

304. Li L, Yu H, Schumacher F, Casey G, Witte JS. Relation of serum insulin-like growth factor-I (IGF-I) and IGF binding protein-3 to risk of prostate cancer (United States). Cancer Causes Control. 2003 Oct;14(8):721-6
305. Chokkalingam AP, Pollak M, Fillmore CM, Gao YT, Stanczyk FZ, Deng J, Sesterhenn IA, Mostofi FK, Fears TR, Madigan MP, Ziegler RG, Fraumeni JF Jr, Hsing AW. Insulin-like growth factors and prostate cancer: a population-based case-control study in China. Cancer Epidemiol Biomarkers Prev. 2001 May;10(5):421-7
306. Harman SM, Metter EJ, Blackman MR, Landis PK, Carter HB. Baltimore Longitudinal Study on Aging. Serum levels of IGF-I, IGF-II, IGF-BP-3, and PSA as predictors of clinical prostate cancer. J Clin Endocrinol Metab. 2000 Nov;85(11):4258-65

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)*
307. Emerman JT, Leahy M, Gout PW, Bruchovsky N. Elevated growth hormone levels in sera from breast cancer patients. Horm Metab Res. 1985 Aug;17(8):421-4

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
308. Yu H, Li BD, Smith M, Shi R, Berkel HJ, Kato I.. Polymorphic CA repeats in the IGF-I gene and breast cancer. Breast Cancer Res Treat. 2001 Nov;70(2):117-22
309. Vadgama JV, Wu Y, Datta G, Khan H, Chillar R. Plasma insulin-like growth factor-I and serum IGF-binding protein 3 can be associated with the progression of breast cancer, and predict the risk of recurrence and the probability of survival in African-American and Hispanic women. Oncology. 1999 Nov;57(4):330-40 *(up to 7x greater breast cancer incidence in women in the highest quintile of serum IGF-1: serum IGFBP-3 ratio compared to women in the lowest quintile)*

A study where a lower serum IGF-BP-3 was found in breast cancer patients
310. Bruning PF, Van Doorn J, Bonfrer JM, Van Noord PA, Korse CM, Linders TC, Hart AA. Insulin-like growth-factor-binding protein 3 is decreased in early-stage operable pre-menopausal breast cancer. Int J Cancer. 1995 Jul 28;62(3):266-70

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)*
311. Ma J, Pollak MN, Giovannucci E, Chan JM, Tao Y, Hennekens CH, Stampfer MJ. Prospecftive study of colorectal cancer risk in men and plasma levels of IGF-1 and IGF-BP-3. J Natl Cancer Inst. 1999; 91: 620-5

In acromegaly, the incidence of and/or mortality from digestive cancer is increased
312. Ron E, Gridley G, Hrubec Z, Page W, Arora S, Fraumeni JF Jr. Acromegaly and gastrointestinal cancer. Cancer. 1991 Oct 15;68(8):1673-7 *(but no increase in overall cancer incidence)*
313. 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 *(but decreased overall incidence of cancer in acromegaly, and no increased overall cancer mortality)*

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. Lamberton 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 ”)
316. Snyder PJ, Bigdeli H, Gardner DF, Mihailovic V, Rudenstein RS, Sterling FH, Utiger RD. Gonadal function in fifty men with untreated pituitary adenomas. J Clin Endocrinol Metab. 1979 Feb;48(2):309-14
317. Valenta LJ, Sostrin RD, Eisenberg H, Tamkin JA, Elias AN. Diagnosis of pituitary tumors by hormone assays and computerized tomography. Am J Med. 1982 Jun;72(6):861-73

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; moreoever, the doses used in childhood are extremely high – at least seven times those used in treatment of GH-deficiency in adults)*

318. Swerdlow AJ, Higgins CD, Adlard P, Preece MA. Risk of cancer in patients treated with human pituitary growth hormone in the UK, 1959-85: a cohort study. Lancet. 2002 Jul 27;360(9329):273-7

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 autotopsy, and premenopausal breast cancer patients who were diagnosed within the 2 years after the first blood sample.*

319. 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

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

320. Chokkalingam AP, Gao YT, Deng J, Stanczyk FZ, Sesterhenn IA, Mostofi FK, Fraumeni JF Jr, Hsing AW. Insulin-like growth factors and risk of benign prostatic hyperplasia. Prostate. 2002 Jul 1;52(2):98-105.
321. Colao A, Marzullo P, Ferone D, Spiezia S, Cerbone G, Marino V, Di Sarno A, Merola B, Lombardi G. Prostatic hyperplasia: an unknown feature of acromegaly. J Clin Endocrinol Metab. 1998 Mar;83(3):775-9

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

322. Ng ST, Zhou J, Adesanya OO, Wang J, LeRoith D, Bondy CA. Growth hormone treatment induces mammary gland hyperplasia in aging primates. Nat Med. 1997 Oct;3(10):1141-4

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

323. Finne P, Auvinen A, Koistinen H, Zhang WM, Maattanen L, Rannikko S, Tammela T, Seppala M, Hakama M, Stenman UH. Insulin-like growth factor I is not a useful marker of prostate cancer in men with elevated levels of prostate-specific antigen. J Clin Endocrinol Metab. 2000 Aug;85(8):2744-77

Bias 3: Serum IGF-I 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)*

324. Dai Q, Xiao-ou Shu, Fan Jin, Yu-Tang Gao, Zhi-Xian Ruan, Zheng W. Consumption of animal foods, cooking methods, and risk of breast cancer. Cancer Epidemiol Biom Prev. 2002;11:801-8

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

325. Zheng W, Deitz AC, Campbell DR, Wen WQ, Cerhan JR, Sellers TA, Folsom AR, Hein DW. N-acetyltransferase 1 genetic polymorphism, cigarette smoking, well-done meat intake, and breast cancer risk. Cancer Epidemiol Biomarkers Prev. 1999 Mar;8(3):233-9
326. Norrish AE, Lynnette R. Ferguson, Mark G. Knize, James S. Felton, Susan J. Sharpe, Jackson RT. Heterocyclic Amine Content of Cooked Meat and Risk of Prostate Cancer. J Nat Cancer Inst. 1999; 91 (23):2038-44
327. Sinha R, Chow WH, Kulldorff M, Denobile J, Butler J, Garcia-Closas M, Weil R, Hoover RN, Rothman N. Well-done, grilled red meat increases the risk of colorectal adenomas. Cancer Res. 1999;59(17):4320-4
328. Butler LM, Sinha R, Millikan RC, Martin CF, Newman B, Gammon MD, Ammerman AS, Sandler RS. Heterocyclic amines, meat intake, and association with colon cancer in a population-based study. Am J Epidemiol. 2003;157(5):434-45

329. Wolk A. Diet, lifestyle and risk of prostate cancer. Acta Oncol. 2005;44(3):277-81
330. Grant WB. An ecologic study of dietary links to prostate cancer. Altern Med Review 1999; 4(3): 162-9 *(in more than 14 European countries)*
331. Cho E, Spiegelman D, Hunter DJ, Chen WY, Stampfer MJ, Colditz GA, Willett WC. Premenopausal fat intake and risk of breast cancer. J Natl Cancer Inst. 2003 Jul 16;95(14):1079-85

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

332. Kaklamani VG, Linos A, Kaklamani E, Markaki I, Koumantaki Y, Mantzoros CS. Dietary fat and carbohydrates are independently associated with circulating insulin-like growth factor 1 and insulin-like growth factor-binding protein 3 concentrations in healthy adults. J Clin Oncol. 1999 Oct;17(10):3291-8
333. Larsson SC, Wolk K, Brismar K, Wolk A. Association of diet with serum insulin-like growth factor I in middle-aged and elderly men. Am J Clin Nutr. 2005 May;81(5):1163-7
334. Allen NE, Appleby PN, Davey GK, Kaaks R, Rinaldi S, Key TJ. The associations of diet with serum insulin-like growth factor I and its main binding proteins in 292 women meat-eaters, vegetarians, and vegans. Cancer Epidemiol Biomarkers Prev. 2002 Nov;11(11):1441-8
335. Hoppe C, Molgaard C, Juul A, Michaelsen KF. High intakes of skimmed milk, but not meat, increase serum IGF-I and IGFBP-3 in eight-year-old boys. Eur J Clin Nutr. 2004 Sep;58(9):1211-6

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.

336. DiGiovanni J, Kiguchi K, Frijhoff A, Wilker E, Bol DK, Beltran L, Moats S, Ramirez A, Jorcano J, Conti C. Deregulated expression of insulin-like growth factor 1 in prostate epithelium leads to neoplasia in transgenic mice. Proc Natl Acad Sci USA. 2000 Mar 28;97(7):3455-60
337. Kaplan PJ, Mohan S, Cohen P, Foster BA, Greenberg NM. The insulin-like growth factor axis and prostate cancer: lessons from the transgenic adenocarcinoma of mouse prostate (TRAMP) model. Cancer Res. 1999 May 1;59(9):2203-9

Bias 5: the variability of serum IGF-1 makes that 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)

338. Milani D, Carmichael JD, Welkowitz J, Ferris S, Reitz RE, Danoff A, Kleinberg DL. Variability and reliability of single serum IGF-I measurements: impact on determining predictability of risk ratios in disease development. J Clin Endocrinol Metab. 2004 May;89(5):2271-4 *("If fasting serum IGF-1 is measured twice, two weeks apart, individuall differences range from -36.25 to +38.24%, while the mean value for the group of 84 shows high correlation between the two IGF-Is (r=0.922; p<0.0001) and varies much less (mean 120 at first visit) versus 115; p=0.03) in normal volunteers between the ages of 50 and 90 years. When considered in quartiles, IGF-I changed from one quartile to another in 34/84 (40.5%) of the volunteers. When the group was divided in halves, tertiles, quartiles, or quintiles there was an increasing number of subjects who changed from one subdivision to another as the number of gradations increased. These results suggest that the predictive outcomes of earlier studies that used single IGF-I samples for analysis of risk ratios according to tertiles, quartiles, or quintiles could have been different if a second IGF-I was used to establish the risk ratio.")*

Arguments pro GH use:

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

Prostate cancer

339. Weiss JM, Huang WY, Rinaldi S, Fears TR, Chatterjee N, Chia D, Crawford ED, Kaaks R, Hayes RB. IGF-1 and IGFBP-3: Risk of prostate cancer among men in the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial. Int J Cancer. 2007 Nov 15;121(10):2267-73

Colorectal cancer

340. Probst-Hensch NM, Yuan JM, Stanczyk FZ, Gao YT, Ross RK, Yu MC. IGF-1, IGF-2 and IGFBP-3 in prediagnostic serum: association with colorectal cancer in a cohort of Chinese men in Shanghai. Br J Cancer. 2001 Nov 30;85(11):1695-9

Breast cancer

341. Del Giudice ME, Fantus IG, Ezzat S, McKeown-Eyssen G, Page D, Goodwin PJ. Insulin and related factors in premenopausal breast cancer risk. Breast Cancer Res Treat 1998 Jan;47(2):111-20 *(No statistically significant differences between breast cancer patients and controls for IGF-I and IGFBP-1 levels in premenopausal women)*

342. Kajdaniuk D, Marek B. Influence of adjuvant chemotherapy with cyclophosphamide methotrexate and 5-fluorouracil on plasma insulin-like growth factor-I and chosen hormones in breast cancer pre-menopausal patients. J Clin Pharm Ther 2000 Feb;25(1):67-72 *(Plasma IGF-I concentration in breast cancer patients prior to treatment did not differ significantly from that of healthy women)*

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)

343. Svensson J, Bengtsson BÅ, Rosén T, Odén A, Johannsson G. Malignant disease and cardiovascular morbidity in hypopituitary adults with or without growth hormone replacement therapy. J Clin Endocrinol Metab. 2004 Jul;89(7):3306-12

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

344. Finne P, Auvinen A, Koistinen H, Zhang WM, Maattanen L, Rannikko S, Tammela T, Seppala M, Hakama M, Stenman UH. Insulin-like growth factor I is not a useful marker of prostate cancer in men with elevated levels of prostate-specific antigen. J Clin Endocrinol Metab. 2000 Aug;85(8):2744-7
345. Woodson K, Tangrea JA, Pollak M, Copeland TD, Taylor PR, Virtamo J, Albanes D. Serum IGF-1: tumor marker or etiologic factor? A prospective study of prostate cancer among Finnish men. Cancer Res. 2003;15;63(14):3991-4 *(- 48 % for men in the highest quartile of serum IGF-1)*
346. Baffa R, Reiss K, El-Gabry EA, Sedor J, Moy ML, Shupp-Byrne D, Strup SE, Hauck WW, Baserga R, Gomella LG. Low serum insulin-like growth factor 1 (IGF-1): a significant association with prostate cancer. Tech Urol 2000 Sep;6(3):236-9

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

347. Agurs-Collins T, Adams-Campbell LL, Kim KS, Cullen KJ.Ins ulin-like growth factor-1 and breast cancer risk in postmenopausal African-American women. Cancer Detect Prev. 2000;24(3):199-206. *(Significant inverse association of serum IGF-1 and cancer stage: higher TNM (tumor-node-metastasis))*

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)*

348. Voskuil DW, Bosma A, Vrieling A, Rookus MA, van 't Veer LJ. Insulin-like growth factor (IGF)-system mRNA quantities in normal and tumor breast tissue of women with sporadic and familial breast cancer risk. Breast Cancer Res Treat. 2004 Apr;84(3):225-33 (*The number of IGF-1 receptors is -61% lower in human breast cancer tissue, -72% lower in sporadic breast cancer and -26% lower in familial breast cancer)*
349. Nardon E, Buda I, Stanta G, Buratti E, Fonda M, Cattin L. Insulin-like growth factor system gene expression in women with type 2 diabetesand breast cancer. J Clin Pathol. 2003 Aug;56(8):599-604. *(Suggested higher risk of breast cancer at low normal levels of gene expression of IGF-1 and IGF-1 receptor in women)*

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 cancer: the higher IGF-BP-3, the lower the cancer risk*

350. Wollmann HA, Schonau E, Blum WF, Meyer F, Kruse K, Ranke MB. Dose-dependent responses in insulin-like growth factors, insulin-like growth factor-binding protein-3 and parameters of bone metabolism to growth hormone therapy in young adults with growth hormone deficiency. Horm Res. 1995;43(6):249-56
351. Grimberg A, Cohen P. GH & prostate cancer: guilty by association? J Endocrinol Invest. 1999;22(5 Suppl):64-73

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

352. Harman SM, Metter EJ, Blackman MR, Landis PK, Carter HB. Baltimore Longitudinal Study on Aging. Serum levels of IGF-I, IGF-II, IGF-BP-3, and PSA as predictors of clinical prostate cancer. J Clin Endocrinol Metab. 2000 Nov;85(11):4258-65

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

353. Svensson J, Bengtsson BÅ, Rosén T, Odén A, Johannsson G. Malignant disease and cardiovascular morbidity in hypopituitary adults with or without growth hormone replacement therapy. J Clin Endocrinol Metab. 2004 Jul;89(7):3306-12

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

354. Berglund A, Gravholt CH, Olsen MS, Christiansen JS, Stochholm K. Growth hormone replacement does not increase mortality in patients with childhood-onset growth hormone deficiency. Clin Endocrinol (Oxf). 2015 Nov;83(5):677-83.
355. Stochholm K, Berglund A, Juul S, Gravholt CH, Christiansen JS. Socioeconomic factors do not but GH treatment does affect mortality in adult-onset growth hormone deficiency. J Clin Endocrinol Metab. 2014 Nov;99(11):4141-8.

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

356. 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.
357. Jenkins PJ, Mukherjee A, Shalet SM. Does growth hormone cause cancer? Clin Endocrinol (Oxf). 2006 Feb;64(2):115-21.

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

358. Tacke J, Bolder U, Herrmann A, Berger G, Jauch KW. Long-term risk of gastrointestinal tumor recurrence after postoperative treatment with recombinant human growth hormone. JPEN J Parenter Enteral Nutr 2000 May-Jun;24(3):140-4 (non-significantly lower mortality (-11%), less recurrence and longer disease-free surviva l for patients treated with GH.

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

359. Swerdlow AJ, Reddingius RE, Higgins CD, Spoudeas HA, Phipps K, Qiao Z, Ryder WD,Brada M, Hayward RD, Brook CG, Hindmarsh PC, Shalet SM. Growth hormone treatment of children with brain tumors and risk (after 5 years of therapy : -40% less recurrence of brain tumors and -50% less mortality or children with GH therapy)

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

360. van Varsseveld NC, van Bunderen CC, Franken AA, Koppeschaar HP, van der Lely AJ, Drent ML. Tumor Recurrence or Regrowth in Adults With Nonfunctioning Pituitary Adenomas Using GH Replacement Therapy. J Clin Endocrinol Metab. 2015 Aug;100(8):3132-9. doi: 10.1210/jc.2015-1764.
361. Buchfelder M, Kann PH, Wüster C, Tuschy U, Saller B, Brabant G, Kleindienst A,Nomikos P; German KIMS Board. Influence of GH substitution therapy in deficient adults on the recurrence rate of hormonally inactive pituitary adenomas: a case control study. Eur J Endocrinol. 2007 Aug;157(2):149-56.

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

362. Bartlett DL, Charland S, Torosian MH. Growth hormone, insulin, and somatostatin therapy of cancer cachexia. Cancer. 1994 Mar 1;73(5):1499-504

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

363. Torosian MH. Growth hormone and prostate cancer growth and metastasis in tumor-bearing animals. J Pediatr Endocrinol. 1993 Jan-Mar;6(1):93-7

A lower serum GH level is found in gastric cancer patients

364. Colombo F, Iannotta F, Fachinetti A, Giuliani F, Cornaggia M, Finzi G, Mantero G, Fraschini F, Malesci A, Bersani M, et al. [Changes in hormonal and biochemical parameters in gastric adenocarcinoma] Minerva Endocrinol. 1991 Jul-Sep;16(3):127-39

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

365. Liao D, Porsch-Hallstrom I, Gustafsson JA, Blanck A. Sex differences at the initiation stage of rat liver carcinogenesis—influence of growth hormone. Carcinogenesis. 1993 Oct;14(10):2045-9

IGF-1-therapy preserved lean mass in rats with sarcoma and cachexia

366. Ng EH, Rock CS, Lazarus DD, Stiaino-Coico L, Moldawer LL, Lowry SF. Insulin-like growth factor I preserves host lean tissue mass in cancer cachexia. Am J Physiol. 1992 Mar;262(3 Pt 2):R426-31

No significant associations of serum levels and prostate cancer risk

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

367. Yu H, Nicar MR, Shi R, Berkel HJ, Nam R, Trachtenberg J, Diamandis EP. Levels of IGF-I and IGF BP- 2 and -3 in serial postoperative serum samples and risk of prostate cancer recurrence. Urology. 2001 Mar;57(3):471-5.
368. Hill M, Bilek R, Safarik L, Starka L. Analysis of relations between serum levels of epitestosterone, estradiol, testosterone, IGF-1 and prostatic specific antigen in men with benign prostatic hyperplasia and carcinoma of the prostate. Physiol Res. 2000;49 Suppl 1:S113-8
369. Kurek R, Tunn UW, Eckart O, Aumuller G, Wong J, Renneberg H. The significance of serum levels of insulin-like growth factor-1 in patients with prostate cancer. BJU Int. 2000 Jan;85(1):125-9
370. Cutting CW, Hunt C, Nisbet JA, Bland JM, Dalgleish 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
372. Woodson K, Tangrea JA, Pollak M, Copeland TD, Taylor PR, Virtamo J, Albanes D. Serum insulin-like growth factor I: tumor marker or etiologic factor? A prospective study of prostate cancer among Finnish men. Cancer Res. 2003 Jul 15;63(14):3991-4
373. Ismail A H, Pollak M, Behlouli H, Tanguay S, Begin LR, Aprikian AG. Insulin-like growth factor-1 and insulin-like growth factor binding protein-3 for prostate cancer detection in patients undergoing prostate biopsy. J Urol. 2002 Dec;168(6):2426-30
374. Bubley GJ, Balk SP, Regan MM, Duggan S, Morrissey ME, Dewolf WC, Salgami E, Mantzoros C. Serum levels of insulin-like growth factor-1 and insulin-like growth factor-1 binding proteins after radical prostatectomy. J Urol. 2002 Nov;168(5):2249-52
375. DeLellis K, Rinaldi S, Kaaks RJ, Kolonel LN, Henderson B, Le Marchand L. Dietary and lifestyle correlates of plasma insulin-like growth factor-I (IGF-I) and IGF binding protein-3 (IGFBP-3): the multiethnic cohort. Cancer Epidemiol Biomarkers Prev. 2004 Sep;13(9):1444-51.

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.*

376. J. Svensson, B.-Å. Bengtsson, T. Rosén, Odén A, Johannsson G. Malignant Disease and Cardiovascular Morbidity in Hypopituitary Adults with or without GH Replacement Therapy . J Clin Endocrinol Metab. 2004 Jul;89(7):3306-12
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

378. 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
379. DeLellis K, Rinaldi S, Kaaks RJ, Kolonel LN, Henderson B, Le Marchand L. Dietary and lifestyle correlates of plasma insulin-like growth factor-I (IGF-I) and IGF binding protein-3 (IGFBP-3): the multiethnic cohort. Cancer Epidemiol Biomarkers Prev. 2004 Sep;13(9):1444-51.

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

380. Wennbo H, Gebre-Medhin M, Gritli-Linde A, Ohlsson C, Isaksson OG, Tornell J. Activation of the prolactin receptor but not the growth hormone receptor is important for induction of mammary tumors in transgenic mice. J Clin Invest. 1997 Dec 1;100(11):2744-51
381. Wennbo H, Tornell J. The role of prolactin and GH in breast cancer. Octogene. 2000;19:1072-6

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

383. Writing group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women. JAMA. 2002; 288: 321-333
384. Beral V; Million Women Study Collaborators. Breast cancer and hormone-replacement therapy in the Million Women Study. Lancet. 2003 Aug 9;362(9382):419-27
385. Persson I, Thurfjell E, Bergstrom R, Holmberg L. Hormone replacement therapy and the risk of breast cancer. Nested case-controlstudy in a cohort of Swedish women attending mammography screening. Int J Cancer 1997 Sep 4;72(5):758-61
386. Schairer C, Lubin J, Troisi R, Sturgeon S, Brinton L, Hoover R. Menopausal estrogen and estrogen-progestin replacement therapy and breast cancer risk. JAMA 2000 Jan 26;283(4):485-91
387. LeBlanc ES, Viscoli CM, Henrich JB. Postmenopausal estrogen replacement therapy is associated with adverse breast. J Womens Health Gend Based Med 1999 Jul-Aug;8(6):815-23
388. Ross RK, Paganini-Hill A, Wan PC, Pike MC. Effect of hormone replacement therapy on breast cancer risk: estrogen versus estrogen plus progestin. J Natl Cancer Inst 2000 Feb 16;92(4):328-32
389. Vessey MP. Effect of endogenous and exogenous hormones on breast cancer: epidemiology. Verh Dtsch Ges Pathol 1997;81:493-501

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; cirtic: 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 cance, 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

391. Meilahn EN, De Stavola B, Allen DS, Fentiman I, Bradlow HL, Sepkovic DW, Kuller LH. Do urinary oestrogen metabolites predict breast cancer? Guernsey III cohort follow-up. Br J Cancer. 1998 Nov;78(9):1250-5

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

392. Seeger H, Mueck AO, Lippert TH. Effect of norethisterone acetate on estrogen metabolism in postmenopausal women. Horm Metab Res. 2000 Oct;32(10):436-9

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

393. Fahraeus L, Larsson-Cohn U. Oestrogens, gonadotrophins and SHBG during oral and cutaneous administration of oestradiol-17 beta to menopausal women. Acta Endocrinol (Copenh). 1982 Dec;101(4):592-6

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

394. Sitruk-Ware R, Plu-Bureau G. Progestins and cancer. Gynecol Endocrinol. 1999 Jun;13 Suppl 4:3-9 Department of Endocrinology, Hôpital Saint-Antoine, Paris.
395. Fournier A, Berrino F, Riboli E, Avenel V, Clavel-Chapelon F. Breast cancer risk in relation to different types of hormone replacement therapy in the E3N-EPIC cohort. Int J Cancer. 2005 Apr 10;114(3):448-54

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)

396. Clarkson TB. Progestogens and cardiovascular disease. A critical review. J Reprod Med. 1999 Feb;44(2 Suppl):180-4
397. Lahdenpera S, Puolakka J, Pyorala T, Luotola H, Taskinen MR. Effects of postmenopausal estrogen/progestin replacement therapy on LDL particles; comparison of transdermal and oral treatment regimens. Atherosclerosis. 1996 May;122(2):153-62
398. Wakatsuki A, Sagara Y.Effects of continuous medroxyprogesterone acetate on lipoprotein metabolism in postmenopausal women receiving estrogen. Maturitas. 1996 Aug;25(1):35-44
399. Cerquetani E, Leonardo F, Pagnotta P, Galetta P, Onorati D, Fini M, Rosano GM. Anti-ischemic effect of chronic oestrogen replacement therapy alone or in combination with medroxyprogesterone acetate in different replacement schemes. Maturitas. 2001 Sep 28;39(3):245-51
400. Duvernoy CS, Rattenhuber J, Seifert-Klauss V, Bengel F, Meyer C, Schwaiger M. Myocardial blood flow and flow reserve in response to short-term cyclical hormone replacement therapy in postmenopausal women. J Gend Specif Med. 2001;4(3):21-7,47
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
402. Mueck AO, Seeger H, Wallwiener D. Medroxyprogesterone acetate versus norethisterone: effect on estradiol-induced changes of markers for endothelial function and atherosclerotic plaque characteristics in human female coronary endothelial cell cultures. Menopause 2002 Jul;9(4):273-281
403. Wakatsuki A, Okatani Y, Ikenoue N, Fukaya T. Effect of medroxyprogesterone acetate on endothelium-dependent vasodilation in postmenopausal women receiving estrogen. Circulation 2001 Oct 9;104(15):1773-8
404. Register TC, Adams MR, Golden DL, Clarkson TB. Conjugated equine estrogens alone, but not in combination with medroxyprogesterone acetate, inhibit aortic connective tissue remodeling after plasma lipid lowering in female monkeys. Arterioscler Thromb Vasc Biol 1998 Jul;18(7):1164-71
405. Miyagawa K, Rosch J, Stanczyk F, Hermsmeyer K. Medroxyprogesterone interferes with ovarian steroid protection against coronary vasospasm. Nat Med 1997 Mar;3(3):324-7
406. Adams MR, Register TC, Golden DL, Wagner JD, Williams JK. Medroxyprogesterone acetate antagonizes inhibitory effects of conjugated equine estrogens on coronary artery atherosclerosis. Arterioscler Thromb Vasc Biol 1997 Jan;17(1):217-21
407. Luckas MJ, Gleeve T, Biljan MM, Buckett WM, Aird IA, Drakeley A, Kingsland CR. The effect of progestagens on the carotid artery pulsatility index in postmenopausal women on oestrogen replacement therapy. Eur J Obstet Gynecol Reprod Biol. 1998 Feb;76(2):221-4
408. Gorodeski GI, Yang T, Levy MN, Goldfarb J, Utian WH. Modulation of coronary vascular resistance in female rabbits by estrogen and progesterone. J Soc Gynecol Investig. 1998 Jul-Aug;5(4):197-202

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

409. Johnson JV, Davidson M, Archer D, Bachmann G. Postmenopausal uterine bleeding profiles with two forms of continuous combined hormone replacement therapy. Menopause. 2002 Jan-Feb;9(1):16-22

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

410. Miyagawa K, Vidgoff J, Hermsmeyer K. Ca2+ release mechanism of primate drug-induced coronary vasospasm. Am J Physiol. 1997 Jun;272(6 Pt 2):H2645-54
411. Minshall RD, Stanczyk FZ, Miyagawa K, Uchida B, Axthelm M, Novy M, Hermsmeyer K. Ovarian steroid protection against coronary artery hyperreactivity in rhesus monkeys. J Clin Endocrinol Metab. 1998 Feb;83(2):649-59
412. 3) Seeger H, Wallwiener D, Mueck AO. Effect of medroxyprogesterone acetate and norethisterone on serum-stimulated and estradiol-inhibited proliferation of human coronary artery smooth muscle cells. Menopause. 2001 Jan-Feb;8(1):5-9

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

413. Seeger H, Wallwiener D, Mueck AO. Effect of medroxyprogesterone acetate and norethisterone on serum-stimulated and estradiol-inhibited proliferation of human coronary artery smooth muscle cells. Menopause. 2001 Jan-Feb;8(1):5-9
414. Sitruk-Ware R. Progestins and cardiovascular risk markers. Steroids. 2000 Oct-Nov;65(10-11):651-8

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

415. Paris JM, Williams KJ, Hermsmeyer KR, Delansorne R. Nomegestrol acetate and vascular reactivity: nonhuman primate experiments. Steroids. 2000 Oct-Nov;65(10-11):621-7

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

416. Hulley S, Grady D, Bush T, Furberg C, Herrington D, Riggs B, Vittinghoff E. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. Heart and Estrogen/progestin Replacement Study (HERS) Research Group. JAMA. 1998 Aug 19;280(7):605-13

417. Levesque H, Courtois H. Estrogen therapy and venous thromboembolic disease. Rev Med Interne. 1997;18 Suppl 6:620s-625s

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

418. Stevenson JC. Hormone replacement therapy and cardiovascular disease revisited. Menopause Int. 2009 Jun;15(2):55-7.

419. Creasman WT. Is there an association between hormone replacement therapy and breast cancer? J Womens Health 1998 Dec;7(10):1231-46

420. Sitruk-Ware R Hormone therapy of menopause and risk of breast cancer. Polemics and Controversies. Presse Med 1994 Jan 8-15;23(1):38-42

421. Franceschi S. Replacement therapy in menopause and risk for breast tumors. Ann Ist Super Sanita 1997;33(2):207-11

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

422. Anderson GL, Limacher M, Assaf AR, Bassford T, Beresford SA, Black H, Bonds D, Brunner R, Brzyski R, Caan B, Chlebowski R, Curb D, Gass M, Hays J, Heiss G, Hendrix S, Howard BV, Hsia J, Hubbell A, Jackson R, Johnson KC, Judd H, Kotchen JM, Kuller L, LaCroix AZ, Lane D, Langer RD, Lasser N, Lewis CE, Manson J, Margolis K, Ockene J, O'Sullivan MJ, Phillips L, Prentice RL, Ritenbaugh C, Robbins J, Rossouw JE, Sarto G, Stefanick ML, Van Horn L, Wactawski-Wende J, Wallace R, Wassertheil-Smoller S; Women's Health Initiative Steering Committee. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. JAMA. 2004 Apr 14;291(14):1701-12.

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

423. Manson JE, Allison MA, Rossouw JE, Carr JJ, Langer RD, Hsia J, Kuller LH, Cochrane BB, Hunt JR, Ludlam SE, Pettinger MB, Gass M, Margolis KL, Nathan L, Ockene JK, Prentice RL, Robbins J, Stefanick ML; WHI and WHI-CACS Investigators. Estrogen therapy and coronary-artery calcification. N Engl J Med. 2007 Jun 21;356(25):2591-602.

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

425. Wild RA, Wu C, Curb JD, Martin LW, Phillips L, Stefanick M, Trevisan M, Manson JE. Coronary heart disease events in the Women's Health Initiative hormone trials: effect modification by metabolic syndrome: a nested case-control study within the Women's Health Initiative randomized clinical trials. Menopause. 2013 Mar;20(3):254-60.

426. LaCroix AZ, Chlebowski RT, Manson JE, Aragaki AK, Johnson KC, Martin L, Margolis KL, Stefanick ML, Brzyski R, Curb JD, Howard BV, Lewis CE, Wactawski-Wende J; WHI Investigators. Health outcomes after stopping conjugated equine estrogens among postmenopausal women with prior hysterectomy: a randomized controlled trial. JAMA. 2011 Apr 6;305(13):1305-14.

Oral medroxyprogesterone acetate causes cardiac isks

427. 9: Kuhl H, Stevenson J. The effect of medroxyprogesterone acetate on estrogen-dependent risks and benefits--an attempt to interpret the Women's Health Initiative results. Gynecol Endocrinol. 2006 Jun;22(6):303-17.

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

428. Hendrix SL, Wassertheil-Smoller S, Johnson KC, Howard BV, Kooperberg C, Rossouw JE, Trevisan M, Aragaki A, Baird AE, Bray PF, Buring JE, Criqui MH, Herrington D, Lynch JK, Rapp SR, Torner J; WHI Investigators. Effects of conjugated equine estrogen on stroke in the Women's Health Initiative. Circulation. 2006 May 23;113(20):2425-34.

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. 11: 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

430. 12: Klaiber EL, Vogel W, Rako S. A critique of the Women's Health Initiative hormone therapy study. Fertil Steril. 2005 Dec;84(6):1589-601.

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)

2-a) 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-dihydroequilin, 17 alpha-estradiol, 17 a-dihydroequilenin and numerous other horse estrogens

431. Morgan MR, Whittaker PG, Dean PD, Lenton EA, Sexton L, Cooke ID. Plasma equilin concentrations in an oophorectomized woman following ingestion of conjugated equine oestrogens (Premarin). Eur J Clin Invest. 1979 Dec;9(6):473-4
432. Bhavnani BR, Sarda IR, Woolever CA. Radioimmunoassay of plasma equilin and estrone in postmenopausal women after the administration of premarin. J Clin Endocrinol Metab. 1981 Apr;52(4):741-7
433. Utian WH, Katz M, Davey DA, Carr PJ. Effect of premenopausal castration and incremental dosages of conjugated equine estrogens on plasma follicle-stimulating hormone, luteinizing hormone, and estradiol. Am J Obstet Gynecol. 1978 Oct 1;132(3):297-302

Treatments with ethinylestradiol (the Million women study):

434. Goldzieher JW. Selected aspects of the pharmacokinetics and metabolism of ethinyl estrogens and their clinical implications. Am J Obstet Gynecol. 1990 Jul;163(1 Pt 2):318-22
435. Shenfield GM, Griffin JM. Clinical pharmacokinetics of contraceptive steroids. An update. Clin Pharmacokinet. 1991 Jan;20(1):15-37.

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-1) 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)

436. Powers MS, Schenkel L, Darley PE, Good WR, Balestra JC, Place VA. Pharmacokinetics and pharmacodynamics of transdermal dosage forms of 17-beta-estradiol: comparison with conventional oral estrogens used for hormone replacement. Am J Obstet Gynecol. 1985 Aug 15;152(8):1099-106
437. Chetkowski RJ, Meldrum DR, Steingold KA, Randle D, Lu JK, Eggena P, Hershman JM, Alkjaersig NK, Fletcher AP, Judd HL. Biologic effects of transdermal estradiol. N Engl J Med. 1986 Jun 19;314(25):1615-20

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 accumulate. The liver produces under this "estrogen dominance" excessive amounts of hormone plasma bnding 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.

438. Stumpf PG. Pharmacokinetics of estrogen. Obstet Gynecol. 1990 Apr;75(4 Suppl):9S-14S; discussion 15S-17S

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

439. Wolthers T, Hoffman DM, Nugent AG, Duncan MW, Umpleby M, Ho KK. Oral estrogen antagonizes the metabolic actions of growth hormone in growth hormone-deficient women. Am J Physiol Endocrinol. Metab. 2001 Dec;281(6):E1191-6
440. Paassilta M, Karjalainen A, Kervinen K, Savolainen MJ, Heikkinen J, Backstrom AC, Kesaniemi YA. Insulin-like growth factor binding protein-1 (IGFBP-1) and IGF-I during oral and transdermal estrogen replacement therapy: relation to lipoprotein(a) levels. Atherosclerosis. 2000 Mar;149(1):157-62
441. Janssen YJ, Helmerhorst F, Frolich 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
442. Cook DM, Ludlam WH, Cook MB. Route of estrogen administration helps to determine growth hormone (GH) replacement dose in GH-deficient adults. J Clin Endocrinol Metab. 1999 Nov;84(11):3956-60
443. Cano A, Castelo-Branco C, Tarin JJ. Effect of menopause and different combined estradiol-progestin regimens on basal and growth hormone-releasing hormone-stimulated serum growth hormone, insulin-like growth factor-1, insulin-like growth factor binding protein (IGFBP)-1, and IGFBP-3 levels. Fertil Steril. 1999 Feb;71(2):261-7
444. Bellantoni MF, Vittone J, Campfield AT, Bass KM, Harman SM, Blackman MR. Effects of oral versus transdermal estrogen on the growth hormone/insulin-like growth factor I axis in younger and older postmenopausal women: a clinical research center study. J Clin Endocrinol Metab. 1996 Aug;81(8):2848-53
445. Ho KK, Weissberger AJ. Impact of short-term estrogen administration on growth hormone secretion and action: distinct route-dependent effects on connective and bone tissue metabolism.J Bone Miner Res. 1992 Jul;7(7):821-7
446. Weissberger AJ, Ho KK, Lazarus L. Contrasting effects of oral and transdermal routes of estrogen replacement therapy on 24-hour growth hormone (GH) secretion, insulin-like growth factor I, and GH-binding protein in postmenopausal women. J Clin Endocrinol Metab 1991 Feb;72(2):374-81

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

447. Luboshitzky R, Shen-Orr Z, Herer P, Nave R. Urinary 6-sulfatoxymelatonin excretion in hyperandrogenic women with polycystic ovary syndrome: the effect of ethinyl estradiol-cyproterone acetate treatment. Gynecol Endocrinol. 2003 Dec;17(6):441-7

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

448. Rudorff KH, Herrmann J, Dieterich T, Kruskemper HL. Effect of estrogen upon thyroid metabolism. Med Klin. 1978 Aug 4;73(31):1109-13

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

449. Hammerstein J, Daume E, Simon A, Winkler UH, Schindler AE, Back DJ, Ward S, Neiss A. Influence of gestodene and desogestrel as components of low-dose oral contraceptives on the pharmacokinetics of ethinyl estradiol (EE2), on serum CBG and on urinary cortisol and 6 beta-hydroxycortisol. Contraception. 1993 Mar;47(3):263-81

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

450. Coenen CM, Thomas CM, Borm GF, Rolland R. Comparative evaluation of the androgenicity of four low-dose, fixed-combination oral contraceptives. Int J Fertil Menopausal Stud. 1995;40 Suppl 2:92-7

451. De Lignieres B, Basdevant A, Thomas G, Thalabard JC, Mercier-Bodard C, Conard J, Guyene TT, Mairon N, Corvol P, Guy-Grand B, et al. Biological effects of estradiol-17 beta in postmenopausal women: oral versus percutaneous administration. J Clin Endocrinol Metab. 1986 Mar;62(3):536-41

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

452. Heger-Mahn D, Warlimont C, Faustmann T, Gerlinger C, Klipping C. Combined ethinylestradiol/gestodene contraceptive patch: two-center, open-label study of ovulation inhibition, acceptability and safety over two cycles in female volunteers. Eur J Contracept Reprod Health Care. 2004 Sep;9(3):173-81))

2c-1) The transdermal contraceptive patch (Ortho Evra/Evra**,** 1 patch per week **of 20 µg e**thinyl 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

453. Devineni D, Skee D, Vaccaro N, Massarella J, Janssens L, LaGuardia KD, Leung AT. Pharmacokinetics and pharmacodynamics of a transdermal contraceptive patch and an oral contraceptive. J Clin Pharmacol. 2007 Apr;47(4):497-509.

The transdermal contraceptive patch provides a higher level of SHBG and similar lowering effect on key serum androgen levels (DHEAs, free testosterone and androstanediol glucuronide) as oral contraceptive pills

454. White T, Jain JK, Stanczyk FZ. Effect of oral versus transdermal steroidal contraceptives on androgenic markers. Am J Obstet Gynecol. 2005 Jun;192(6):2055-9 *(patch versus oral contraceptive: 449% vs 274% increase in SHBG; -40 % vs -39% reduction of free testosterone, -26% versus – 32 % reduction in DHEA sulphate, and – 52 % versus -51% reduction in androstanediol glucuronide)*

The transdermal contraceptive patch provides higher levels of SHBG and TBG and greater increase of CRP compared to the oral pill

455. White T, Ozel B, Jain JK, Stanczyk FZ. Effects of transdermal and oral contraceptives on estrogen-sensitive hepatic proteins. Contraception. 2006 Oct;74(4):293-6

The transdermal contraceptive patch causes a higher incidence of breast pain, dysmenorrhoea and application site reactions than the oral pill

456. Radowicki S, Skorzewska K, Szlendak K. [Safety evaluation of a transdermal contraceptive system with an oral contraceptive] Ginekol Pol. 2005 Nov;76(11):884-9.

The transdermal contraceptive patch causes a similar increase in risk of nonfatal venous thromboembolism for the contraceptive patch as for the oral contraceptive pills

457. Jick SS, Kaye JA, Russmann S, Jick H. Risk of nonfatal venous thromboembolism in women using a contraceptive transdermal patch and oral contraceptives containing norgestimate and 35 micrograms of ethinyl estradiol. Contraception. 2006 Mar;73(3):223-8

The transdermal contraceptive patch causes similar unfavourable lipid changes: increases in total cholesterol and total triglycerides compared to the oral group

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 ethynylestradiol to the body

458. van den Heuvel MW, van Bragt AJ, Alnabawy AK, Kaptein MC.Comparison of ethinylestradiol pharmacokinetics in three hormonal contraceptive formulations: the vaginal ring, the transdermal patch and an oral contraceptive. Contraception. 2005 Sep;72(3):168-74.

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

459. Nozaki M, Ogata R, Koera K, Hashimoto K, Nakano H. Changes in coagulation factors and fibrinolytic components of postmenopausal women receiving continuous hormone replacement therapy. Climacteric. 1999 Jun;2(2):124-30

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

460. Luyer MD, Khosla S, Owen WG, Miller VM. Prospective randomized study of effects of unopposed estrogen replacement therapy on markers of coagulation and inflammation in postmenopausal women. J Clin Endocrinol Metab. 2001 Aug;86(8):3629-34

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

461. Alkjaersig N, Fletcher AP, de Ziegler D, Steingold KA, Meldrum DR, Judd HL. Blood coagulation in postmenopausal women given estrogen treatment: comparison of transdermal and oral administration. J Lab Clin Med. 1988 Feb;111(2):224-8

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

462. Lobo RA, Bush T, Carr BR, Pickar JH. Effects of lower doses of conjugated equine estrogens and medroxyprogesterone acetate on plasma lipids and lipoproteins, coagulation factors, and carbohydrate metabolism. Fertil Steril. 2001 Jul;76(1):13-24
463. Bonduki CE, Lourenco DM, Baracat E, Haidar M, Noguti MA, da Motta EL, Lima GR. Effect of estrogen-progestin hormonal replacement therapy on plasma antithrombin III of postmenopausal women. Acta Obstet Gynecol Scand. 1998 Mar;77(3):330-3

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

464. Zanger D, Yang BK, Ardans J, Waclawiw MA, Csako G, Wahl LM, Cannon RO 3rd. Divergent effects of hormone therapy on serum markers of inflammation in postmenopausal women with coronary artery disease on appropriate medical management. J Am Coll Cardiol 2000 Nov 15;36(6):1797-802

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

465. Oger E, Scarabin PY. Assessment of the risk for venous thromboembolism among users of hormone replacement therapy. Drugs Aging. 1999 Jan;14(1):55-61

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

466. Oger E, Scarabin PY. Hormone replacement therapy in menopause and the risk of cerebrovascular accident. Ann Endocrinol (Paris). 1999 Sep;60(3):232-41

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

467. Prelevic GM, Kwong P, Byrne DJ, Jagroop IA, Ginsburg J, Mikhailidis DP. A cross-sectional study of the effects of hormon replacement therapy on the cardiovascular disease risk profile in healthy postmenopausal women. Fertil Steril. 2002 May;77(5):945-51
468. Decensi A, Omodei U, Robertson C, Bonanni B, Guerrieri-Gonzaga A, Ramazzotto F, Johansson H, Mora S, Sandri MT, Cazzaniga M, Franchi M, Pecorelli S. Effect of transdermal estradiol and oral conjugated estrogen on C-reactive protein in retinoid-placebo trial in healthy women. Circulation. 2002 Sep 3;106(10):1224-8

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

469. Kerdelhue B, Jolette J. The influence of the route of administration of 17beta-estradiol, intravenous (pulsed) versus oral, upon DMBA-induced mammary tumour development in ovariectomised rats. Breast Cancer Res Treat. 2002 May;73(1):13-22

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

470. Foidart JM, Colin C, Denoo X, Desreux J, Beliard A, Fournier S, de Lignieres B. Estradiol and progesterone regulate the proliferation of human breast epithelial cells. Fertil Steril. 1998 May;69(5):963-9

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)*

471. de Lignieres B, de Vathaire F, Fournier S, Urbinelli R, Allaert F, Le MG, Kuttenn F. Combined hormone replacement therapy and risk of breast cancer in a French cohort study of 3175 women. Climacteric. 2002 Dec;5(4):332-40

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

Studies where high levels of endogenous BIO-IDENTICAL estrogens are associated with a lower incidence of cancer or longer survival after breast cancer

472. Holmberg L, Norden T, Lindgren A, Wide L, Degerman M, Adami HO. Pre-operative oestradiol levels - relation to survival in breast cancer. Eur J Surg Oncol. 2001 Mar;27(2):152-6
473. MacMahon B, Cole P, Brown JB, Aoki K, Lin TM, Morgan RW, Woo NC. Urine oestrogen profiles of Asian and North American women. Int J Cancer. 1974 Aug 15;14(2):161-7
474. MacMahon B, Cole P, Brown JB, Aoki K, Lin TM, Morgan RW, Woo N. Oestrogen profiles of Asian and North American women. Lancet. 1971 Oct 23;2(7730):900-2
475. Ursin G, Wilson M, Henderson BE, Kolonel LN, Monroe K, Lee HP, Seow A, YuMC, Stanczyk FZ, Gentzschein E Do urinary estrogen metabolites reflect the differences in breast cancer risk between Singapore Chinese and United States African-American and white women? Cancer Res. 2001 Apr 15;61(8):3326-9
476. Ursin G, London S, Stanczyk FZ, Gentzschein E, Paganini-Hill A, Ross RK, Pike MC. Urinary 2-hydroxyestrone/16alpha-hydroxyestrone ratio and risk of breast cancer in postmenopausal women. J Natl Cancer Inst. 1999 Jun 16;91(12):1067-72
477. Lemon HM. Pathophysiologic considerations in the treatment of menopausal patients withoestrogens; the role of oestriol in the prevention of mammary carcinoma. Acta Endocrinol Suppl. (Copenh). 1980;233:17-27
478. Vorherr H, Messer RH. Breast cancer: potentially predisposing and protecting factors. Role of pregnancy, lactation, and endocrine status. Am J Obstet Gynecol. 1978 Feb 1;130(3):335-58

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

479. Holmberg L, Norden T, Lindgren A, Wide L, Degerman M, Adami HO. Pre-operative oestradiol levels - relation to survival in breast cancer. Eur J Surg Oncol 2001 Mar;27(2):152-6

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

480. Adami HO, Bergstrom R, Holmberg L, Klareskog L, Persson I, Ponten J.The effect of female sex hormones on cancer survival. A register-based study in patients younger than 20 years at diagnosis. JAMA. 1990 Apr 25;263(16):2189-93
481. Adami HO, Holmberg L, Persson I. Survival and age at diagnosis in breast cancer. N Engl J Med. 1987 ; 316(12): 750-2

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

482. MacMahon B, Cole P, Brown JB, Aoki K, Lin TM, Morgan RW, Woo NC. Urine oestrogen profiles of Asian and North American women. Int J Cancer. 1974 Aug 15;14(2):161-7.

483. MacMahon B, Cole P, Brown JB, Aoki K, Lin TM, Morgan RW, Woo N. Oestrogen profiles of Asian and North American women. Lancet. 1971 Oct 23;2(7730):900-2.
484. Ursin G, Wilson M, Henderson BE, Kolonel LN, Monroe K, Lee HP, Seow A, YuMC, Stanczyk FZ, Gentzschein E Do urinary estrogen metabolites reflect the differences in breast cancer risk between Singapore Chinese and United States African-American and white women? Cancer Res. 2001 Apr 15;61(8):3326-9.
485. Ursin G, London S, Stanczyk FZ, Gentzschein E, Paganini-Hill A, Ross RK, Pike MC. Urinary 2-hydroxyestrone/16alpha-hydroxyestrone ratio and risk of breast cancer in postmenopausal women. J Natl Cancer Inst 1999 Jun 16;91(12):1067-72
486. Lemon HM. Pathophysiologic considerations in the treatment of menopausal patients withoestrogens; the role of oestriol in the prevention of mammary carcinoma. Acta Endocrinol Suppl (Copenh) 1980;233:17-27
487. Vorherr H, Messer RH. Breast cancer: potentially predisposing and protecting factors. Role of pregnancy, lactation, and endocrine status. Am J Obstet Gynecol 1978 Feb 1;130(3):335-58

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

488. Salazar-Esquivel EL, Morales-Najar R, Calzada-Sanchez L. Infiltrating duct breast carcinoma: the role of estradiol and progesterone receptors. Ginecol Obstet Mex. 1994 Mar; 62: 85-90
489. Heise E, Gorlich M. Estradiol receptor and prognosis in human breast cancer and its metastases. Neoplasma. 1993;40(1):55-7
490. Nagai MA, Marques LA, Yamamoto L, Fujiyama CT, Brentani MM. Estrogen and progesterone receptor mRNA levels in primary breast cancer: association with patient survival and other clinical and tumor features. Int J Cancer. 1994 Nov 1; 59(3): 351-6
491. Mason BH, Holdaway IM, Mullins PR, Yee LH, Kay RG.Progesterone and estrogen receptors as prognostic variables in breast cancer. Cancer Res 1983 Jun;43(6):2985-90
492. Genazzani AR, Gadducci A, Gambacciani M.Controversial issues in climacteric medicine II. Hormone replacement therapy and cancer. International Menopause Society Expert Workshop. 9-12 June 2001, Operadel Duomo, Pisa, Italy. Climacteric 2001 Sep;4(3):181-93

Studies with protective or neutral effects of bio-identical progesterone against breast cancer

5-1) EXOGENOUS BIO-IDENTICAL PROGESTERONE:

Studies where progesterone/progestogen treatment reduced the breast cancer risk in women with breast cysts

493. Plu-Bureau G, Le MG, Sitruk-Ware R, Thalabard JC, Mauvais-Jarvis P. Progestogen use and decreased risk of breast cancer in a cohort study of premenopausal women with benign breast disease. Br J Cancer 1994 Aug;70(2):270-7
494. Plu-Bureau G, Le MG, Thalabard JC, Sitruk-Ware R, Mauvais-Jarvis P. Percutaneous progesterone use and risk of breast cancer: results from a Frenchcohort study of premenopausal women with benign breast disease. Cancer Detect Prev 1999;23(4):290-6 *(the physiological increase of endogenous progesterone during luteal phase coincided with a lower proliferation of breast epithelial cells)*
495. de Lignieres B. Effects of progestogens on the postmenopausal breast. Climacteric. 2002 Sep;5(3):229-35

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

496. Fournier A, Berrino F, Riboli E, Avenel V, Clavel-Chapelon F. Breast cancer risk in relation to different types of hormone replacement therapy in the E3N-EPIC cohort. Int J Cancer. 2005 Apr 10;114(3):448-54

5-2) ENDOGENOUS BIO-IDENTICAL PROGESTERONE:

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

497. Cowan LD, Gordis L, Tonascia JA, Jones GS. Breast cancer incidence in women with a history of progesterone deficiency. Am J Epidemiol 1981 Aug;114(2):209-17
498. Adami HO, Bergstrom R, Holmberg L, Klareskog L, Persson I, Ponten J.The effect of female sex hormones on cancer survival. A register-based study in patients younger than 20 years at diagnosis. JAMA. 1990 Apr 25;263(16):2189-93
499. Adami HO, Holmberg L, Persson I. Survival and age at diagnosis in breast cancer. N Engl J Med. 1987 ; 316(12): 750-2

500. Mohr PE, Wang DY, Gregory WM, Richards MA, Fentiman IS. Serum progesterone and prognosis in operable breast cancer. Br J Cancer. 1996 Jun;73(12):1552-5
501. Badwe RA, Wang DY, Gregory WM, Fentiman IS, Chaudary MA, Smith P, Richards MA, Rubens RD. Serum progesterone at the time of surgery and survival in women with premenopausal operable breast cancer.Eur J Cancer. 1994;30A(4):445-8

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

502. Cooper LS, Gillett CE, Patel NK, Barnes DM, Fentiman IS. Survival of premenopausal breast carcinoma patients in relation to menstrual cycle timing of surgery and estrogen receptor/progesterone receptor status of the primary tumor. Cancer 1999 Nov 15;86(10):2053-8
503. Senie RT, Rosen PP, Rhodes P, Lesser ML.Timing of breast cancer excision during the menstrual cycle influences duration of disease-free survival. Ann Intern Med 1991 Sep 1;115(5):337-42
504. Saad Z, Vincent M, Bramwell V, Stitt L, Duff J, Girotti M, Jory T, Heathcote G, Turnbull I, Garcia B. Timing of surgery influences survival in receptor-negative as well as receptor-positive breast cancer. Eur J Cancer 1994;30A(9):1348-52.
505. Saad Z, Bramwell V, Duff J, Girotti M, Jory T, Heathcote G, Turnbull I, Garcia B, Stitt L.Timing of surgery in relation to the menstrual cycle in premenopausal women with operable breast cancer.: Br J Surg 1994 Feb;81(2):217-20
506. Veronesi U, Luini A, Mariani L, Del Vecchio M, Alvez D, Andreoli C, Giacobone A, Merson M, Pacetti G, Raselli R, et al. Effect of menstrual phase on surgical treatment of breast cancer. Lancet 1994 Jun 18;343(8912):1545-7
507. Holli K, Isola J, Hakama M. Prognostic effect of timing of operation in relation to menstrual phase of breast cancer patient—fact or fallacy. Br J Cancer 1995 Jan;71(1):124-7
508. Love RR, Duc NB, Dinh NV, Shen TZ, Havighurst TC, Allred DC, DeMets DL. Mastectomy and oophorectomy by menstrual cycle phase in women with operable breast cancer. J Natl Cancer Inst 2002 May 1;94(9):662-9
509. Goldhirsch A, Gelber RD, Castiglione M, O'Neill A, Thurlimann B, Rudenstam CM, Lindtner J, Collins J, Forbes J, Crivellari D, Coates A, Cavalli F, Simoncini E, Fey MF, Pagani O, Price K, Senn HJ. Menstrual cycle and timing of breast surgery in premenopausal node-positive breast cancer: results of the International Breast Cancer Study Group (IBCSG) Trial VI. Ann Oncol 1997 Aug;8(8):751-6
510. Vanek VW, Kadivar TF, Bourguet CC. Correlation of menstrual cycle at time of breast cancer surgery to disease-free and overall survival. South Med J 1997 Aug;90(8):780-8
511. Lemon HM, Rodriguez-Sierra JF. Timing of breast cancer surgery during the luteal menstrual phase may improve prognosis. Nebr Med J 1996 Mar;81(3):73-8
512. Badwe RA, Mittra I, Havaldar R. Timing of surgery during the menstrual cycle and prognosis of breast cancer. J Biosci 2000 Mar;25(1):113-2
513. Mangia A, De Lena M, Barletta A, Marzullo F, Attolico M, Stea B, Petroni S, Labriola A, Cellamare G, Digiesi G, Altieri R, Schittulli F, Paradiso A.Timing of breast cancer surgery within the menstrual cycle: tumor proliferative activity, receptor status and short-term clinical outcome. J Exp Clin Cancer Res 1998 Sep;17(3):317-23
514. Tsuchiya A, Furukawa H, Kanno M, Kimijima I, Abe R. Lack of the relationship between menstrual status and timing of surgery in survival of premenopausal patients with breast cancer. Fukushima J Med Sci. 1996 Dec;42(1-2):11-6.
515. Jager W, Sauerbrei W. Effect of timing of surgery during the menstrual cycle of premenopausal breast cancer patients. Breast Cancer Res Treat 1995 Jun;34(3):279-87
516. Zhang B, Shao Y, Wang C. Prognosis of patients with breast cancer related to the timing of operation during menstrual cycle: a report of 218 patients. Zhonghua Zhong Liu Za Zhi 1996 May;18(3):203-7
517. Milella M, Nistico C, Ferraresi V, Vaccaro A, Fabi A, D'Ottavio AM, Botti C, Giannarelli D, Lopez M, Cortesi E, Foggi CM, Antimi M, Terzoli E, Cognetti F, Papaldo P.Breast cancer and timing of surgery during menstrual cycle: a 5-year analysis of 248 premenopausal women. Breast Cancer Res Treat 1999 Jun;55(3):259-6

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

518. Plu-Bureau G, Thalabard JC, Sitruk-Ware R, Asselain B, Mauvais-Jarvis P. Cyclical mastalgia as a marker of breast cancer susceptibility: results of a case-control study among French women. Br J Cancer 1992 Jun;65(6):945-9
519. Deschamps M, Band PR, Coldman AJ, Hislop TG, Longley DJ. Clinical determinants of mammographic dysplasia patterns. Cancer Detect Prev 1996;20(6):610-9
520. Dixon JM, McDonald C, Elton RA, Miller WR. Risk of breast cancer in women with palpable breast cysts: a prospective study. Edinburgh Breast Group. Lancet 1999 May 22;353(9166):1742-5
521. Bruzzi P, Dogliotti L, Naldoni C, Bucchi L, Costantini M, Cicognani A, Torta M, Buzzi GF, Angeli A. Cohort study of association of risk of breast cancer with cyst type in women with gross cystic disease of the breast. BMJ 1997 Mar 29;314(7085):925-8

522. Dupont WD, Page DL, Parl FF, Vnencak-Jones CL, Plummer WD Jr, Rados MS, Schuyler PA. Long-term risk of breast cancer in women with fibroadenoma. N Engl J Med 1994 Jul 7;331(1):10-5

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

523. Hanke H, Hanke S, Ickrath O, Lange K, Bruck B, Muck AO, Seeger H, Zwirner M, Voisard R, Haasis R, Hombach V. Estradiol concentrations in premenopausal women with coronary heart disease. Coron Artery Dis. 1997 Aug-Sep;8(8-9):511-5

524. Bairey Merz CN, Johnson BD, Sharaf BL, Bittner V, Berga SL, Braunstein GD, Hodgson TK, Matthews KA, Pepine CJ, Reis SE, Reichek N, Rogers WJ, Pohost GM, Kelsey SF, Sopko G; WISE Study Group. Hypoestrogenemia of hypothalamic origin and coronary artery disease in premenopausal women: a report from the NHLBI-sponsored WISE study. J Am Coll Cardiol. 2003 Feb 5;41(3):413-9

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

525. Blumel JE, Castelo-Branco C, Leal T, Gallardo L, Saini J, Ferron S, Haya J. Effects of transdermal estrogens on endothelial function in postmenopausal women with coronary disease. Climacteric. 2003 Mar;6(1):38-44

526. Gerhard M, Walsh BW, Tawakol A, Haley EA, Creager SJ, Seely EW, Ganz P, Creager MA. Estradiol therapy combined with progesterone and endothelium-dependent vasodilation in postmenopausal women. Circulation. 1998 Sep 22;98(12):1158-63

527. Gilligan DM, Badar DM, Panza JA, Quyyumi AA, Cannon RO 3rd. Acute vascular effects of estrogen in postmenopausal women. Circulation. 1994 Aug;90(2):786-91

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

528. Lieberman EH, Gerhard MD, Uehata A, Walsh BW, Selwyn AP, Ganz P, Yeung AC, Creager MA. Estrogen improves endothelium-dependent, flow-mediated vasodilation in postmenopausal women. Ann Intern Med. 1994 Dec 15;121(12):936-41.

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

529. Gilligan DM, Quyyumi AA, Cannon RO 3rd. Effects of physiological levels of estrogen on coronary vasomotor function in postmenopausal women. Circulation. 1994 Jun;89(6):2545-51

530. Guetta V, Quyyumi AA, Prasad A, Panza JA, Waclawiw M, Cannon RO 3rd. The role of nitric oxide in coronary vascular effects of estrogen in postmenopausal women. Circulation. 1997 Nov 4;96(9):2795-801

531. Gorodeski GI, Yang T, Levy MN, Goldfarb J, Utian WH. Modulation of coronary vascular resistance in female rabbits by estrogen and progesterone. J Soc Gynecol Investig. 1998 Jul-Aug;5(4):197-202

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

532. Adams MR, Kaplan JR, Manuck SB, Koritnik DR, Parks JS, Wolfe MS, Clarkson TB. Inhibition of coronary artery atherosclerosis by 17-beta estradiol in ovariectomized monkeys. Lack of an effect of added progesterone. Arteriosclerosis. 1990 Nov-Dec;10(6):1051-7

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

533. Kim YD, Chen B, Beauregard J, Kouretas P, Thomas G, Farhat MY, Myers AK, Lees DE. 17 beta-Estradiol prevents dysfunction of canine coronary endothelium and myocardium and reperfusion arrhythmias after brief ischemia/reperfusion. Circulation. 1996 Dec 1;94(11):2901-8

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

534. Delyani JA, Murohara T, Nossuli TO, Lefer AM. Protection from myocardial reperfusion injury by acute administration of 17 beta-estradiol. J Mol Cell Cardiol. 1996 May;28(5):1001-8

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

535. Roque M, Heras M, Roig E, Masotti M, Rigol M, Betriu A, Balasch J, Sanz G. Short-term effects of transdermal estrogen replacement therapy on coronary vascular reactivity in postmenopausal women with angina pectoris and normal results on coronary angiograms. J Am Coll Cardiol. 1998 Jan;31(1):139-43
536. Albertsson PA, Emanuelsson H, Milsom I. Beneficial effect of treatment with transdermal estradiol-17-beta on exercise-induced angina and ST segment depression in syndrome X. Int J Cardiol. 1996 Apr 19;54(1):13-20

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

537. Walsh BA, Mullick AE, Banka CE, Rutledge JC. 17beta-estradiol acts separately on the LDL particle and artery wall to reduce LDL accumulation. J Lipid Res. 2000 Jan;41(1):134-41

Overview on vascular protective effects of estrogen

538. Farhat MY, Lavigne MC, Ramwell PW. The vascular protective effects of estrogen. FASEB J. 1996 Apr;10(5):615-24

Treatments with oral estradiol cause vasodilatation and increased distensibility of arteries

539. Angerer P, Kothny W, Stork S, von Schacky C. Hormone replacement therapy and distensibility of carotid arteries in postmenopausal women: a randomized, controlled trial. J Am Coll Cardiol. 2000 Nov 15;36(6):1789-96

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

540. Sumino H, Ichikawa S, Kasama S, Kumakura H, Takayama Y, Sakamaki T, Kurabayashi M. Effect of transdermal hormone replacement therapy on carotid artery wall thickness and levels of vascular inflammatory markers in postmenopausal women. Hypertens Res. 2005 Jul;28(7):579-84
541. Takahashi K, Tanaka E, Murakami M, Mori-Abe A, Kawagoe J, Takata K, Ohmichi M, Kurachi H. Long-term hormone replacement therapy delays the age related progression of carotid intima-media thickness in healthy postmenopausal women. Maturitas. 2004 Oct 15;49(2):170-7
542. Hashimoto M, Miyao M, Akishita M, Hosoi T, Toba K, Kozaki K, Yoshizumi M, Ouchi Y Effects of long-term and reduced-dose hormone replacement therapy on endothelial function and intima-media thickness in postmenopausal women. Menopause. 2002 Jan-Feb;9(1):58-64

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

543. Meilahn EN. Hemostatic Factors and Ischemic Heart Disease Risk Among Postmenopausal Women. J Thromb Thrombolysis. 1995;1(2):125-131
544. Vehkavaara S, Silveira A, Hakala-Ala-Pietila T, Virkamaki A, Hovatta O, Hamsten A, Taskinen MR, Yki-Jarvinen H. Effects of oral and transdermal estrogen replacement therapy on markers of coagulation, fibrinolysis, inflammation and serum lipids and lipoproteins in postmenopausal women. Thromb Haemost. 2001 Apr;85(4):619-25
545. Tikkanen MJ. The menopause and hormone replacement therapy: lipids, lipoproteins, coagulation and fibrinolytic factors. Maturitas. 1996 Mar;23(2):209-16
546. Scarabin PY, Alhenc-Gelas M, Plu-Bureau G, Taisne P, Agher R, Aiach M. Effects of oral and transdermal estrogen/progesterone regimens on blood coagulation and fibrinolysis in postmenopausal women. A randomized controlled trial. Arterioscler Thromb Vasc Biol. 1997 Nov;17(11):3071-8
547. Akkad AA, Halligan AW, Abrams K, al-Azzawi F.Differing responses in blood pressure over 24 hours in normotensive women receiving oral or transdermal estrogen replacement therapy. Obstet Gynecol. 1997 Jan;89(1):97-103.
548. Nieto JJ, Cogswell D, Jesinger D, Hardiman P. Lipid effects of hormone replacement therapy with sequential transdermal 17-beta-estradiol and oral dydrogesterone. Obstet Gynecol. 2000 Jan;95(1):111-4
549. Perera M, Sattar N, Petrie JR, Hillier C, Small M, Connell JM, Lowe GD, Lumsden MA. The effects of transdermal estradiol in combination with oral norethisterone on lipoproteins, coagulation, and endothelial markers in postmenopausal women with type 2 diabetes: a randomized, placebo-controlled study. J Clin Endocrinol Metab. 2001 Mar;86(3):1140-3
550. Mueck AO, Seeger H, Lippert TH. Effect of transdermal versus oral estradiol administration on the excretion of vasoactive markers in postmenopausal women. Gynakol Geburtshilfliche Rundsch. 2000;40(2):61-7
551. Chen FP, Lee N, Soong YK, Huang KE. Comparison of transdermal and oral estrogen-progestin replacement therapy: effects on cardiovascular risk factors. Menopause. 2001 Sep-Oct;8(5):347-52

I

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

552. Rosano GM, Webb CM, Chierchia S, Morgani GL, Gabraele M, Sarrel PM, de Ziegler D, Collins P. Natural progesterone, but not medroxyprogesterone acetate, enhances the beneficial effect of estrogens on exercise-induced myocardial ischemia in postmenopausal women. J Am Coll Cardiol. 2000 Dec;36(7):2154-9

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

553. Hermsmeyer RK, Mishra RG, Pavcnik D, Uchida B, Axthelm MK, Stanczyk FZ, Burry KA, Illingworth DR, Juan C, Nordt FJ. Prevention of coronary hyperreactivity in preatherogenic menopausal rhesus monkeys by transdermal progesterone. Arterioscler Thromb Vasc Biol. 2004 May;24(5):955-61
554. Minshall RD, Pavcnik D, Browne DL, Hermsmeyer K. Nongenomic vasodilator action of progesterone on primate coronary arteries. J Appl Physiol. 2002 Feb;92(2):701-8

Treatments with intravenous progesterone increase coronary blood flow in pigs

555. Molinari C, Battaglia A, Grossini E, Mary DA, Stoker JB, Surico N, Vacca G. The effect of progesterone on coronary blood flow in anaesthesized pigs. Exp Physiol. 2001 Jan;86(1):101-8

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

556. Jacob MK, White RE. Diazepam, gamma-aminobutyric acid, and progesterone open K(+) channels in myocytes from coronary arteries. Eur J Pharmacol. 2000 Sep 8;403(3):209-19.
557. Crews JK, Khalil RA. Antagonistic effects of 17 beta-estradiol, progesterone, and testosterone on Ca2+ entry mechanisms of coronary vasoconstriction. Arterioscler Thromb Vasc Biol. 1999 Apr;19(4):1034-40
558. Jiang CW, Sarrel PM, Lindsay DC, Poole-Wilson PA, Collins P. Progesterone induces endothelium-independent relaxation of rabbit coronary artery in vitro. Eur J Pharmacol. 1992 Feb 11;211(2):163-7

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

559. Adams MR, Kaplan JR, Manuck SB, Koritnik DR, Parks JS, Wolfe MS, Clarkson TB. Inhibition of coronary artery atherosclerosis by 17-beta estradiol in ovariectomized monkeys. Lack of an effect of added progesterone. Arteriosclerosis. 1990 Nov-Dec;10(6):1051-7
560. Gerhard M, Walsh BW, Tawakol A, Haley EA, Creager SJ, Seely EW, Ganz P, Creager MA. Estradiol therapy combined with progesterone and endothelium-dependent vasodilation in postmenopausal women. Circulation. 1998 Sep 22;98(12):1158-63

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*

561. Axelrod L. Glucocorticoid therapy. Medicine (Baltimore). 1976 Jan;55(1):39-65
562. Axelrod L. Glucocorticoids. In Kelley WN, Harris ED Jr, Ruddy S, Sledge CB (esd); Textbook of Rheumatology, ed 4. Philadelphia: Saunders, 1993
563. Daly JR, Fletcher MR, Glass D, Chambers DJ, Bitensky L, Chayen J. Comparison of effects of long-term corticotrophin and corticosteroid treatment on responses of plasma growth hormone, ACTH, and corticosteroid to hypoglycaemia. Br Med J. 1974 Jun 8;2(918):521-4.
564. Graber AL, Ney RL, Nicholson WE, Island DP, Liddle GW. Natural history of pituitary-adrenal recovery following long-term suppression with corticosteroids. J Clin Endocrinol Metab. 1965 Jan;25:11-6

565. Streck WF, Lockwood DH. Pituitary adrenal recovery following short-term suppression with corticosteroids. Am J Med. 1979 Jun;66(6):910-4 *(-50 % reduction of pituitary-adrenal axis after 5 days of 50 mg/day prednisone, full recovery in 5 days after stopping the 5-day treatment)*
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)*
567. Westerhof L, van Ditmars MJ, Kinderen PJ der, Thijssen JH, Schwarz F. Recovery of adrenocortical function during long-term treatment with corticosteroids. Br Med J. 1970 Nov 28;4(734):534-7
568. Westerhof L, Van Ditmars MJ, Der Kinderen PJ, Thijssen JH, Schwarz F. Recovery of adrenocortical function during long-term treatment with corticosteroids. Br Med J. 1972 Apr 22;2(807):195-7

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

Pharmacological doses are doses above 7.5 mg/day of prednisone

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

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

Studies with adverse effects of glucocortioid treatment on bone density:

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

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

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

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)*

579. Krogsgaard MR, Thamsborg G, Lund B.[Bone loss during low dose glucocorticoid treatment in patients with polymyalgia rheumatica. A double-blind, prospective comparison between prednisolone and deflazacort. Ugeskr Laeger. 1997 Jul 21;159(30):4641-4

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%"; Critic: above 4 mg/day of prednisolone or 20 mg/day of hydrocortisone us, the bone density decreases unless a supplement of anabolic hormones is added)*

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 obviated 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.

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

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

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

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

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

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

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

588. McKenzie R, O'Fallon A, Dale J, Demitrack M, Sharma G, Deloria M, Garcia-Borreguero D, Blackwelder W, Straus SE. Low-dose hydrocortisone for treatment of chronic fatigue syndrome: a randomized controlled trial. JAMA. 1998 Sep 23-30;280(12):1061-6 *("some suppression of adrenal glucocorticoid responsiveness was documented in 12 patients on 30 who received hydrocortisone compared to none in the placebo group")*

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

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

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

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

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

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 methylprednisone for 12-58 months: absence of quantitative bone mass reduction and normal corticotrope reserve were observed even after 58 months of daily steroid administration")*

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

594. Buckley LM, Leib ES, Cartularo KS, Vacek PM, Cooper SM. Effects of low dose corticosteroids on the bone mineral density of patients with rheumatoid arthritis. J Rheumatol. 1995 Jun;22(6):1055-9

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

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

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

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

With DHEA:

596. Papierska L, Rabijewski M, Kasperlik-Załuska 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, McIlwain HH, Freeman PG, Aranow C, Petri MA, Deodhar AA, Blanton E, Manzi S, Kavanaugh 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, Quarles 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

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

With female hormone replacement

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

With GH

604. Kovacs G, Fine RN, Worgall S, Schaefer F, Hunziker EB, Skottner-Lindun A, Mehls O. Growth hormone prevents steroid-induced growth depression in health and uremia. Kidney Int. 1991 Dec;40(6):1032-40.
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 chronic glucocorticoid treatment, GH administration may significantly antagonize several side-effects of long term glucocorticoid administration, such as protein wasting, osteoporosis, and hyperlipidemia, and T-helper/T-suppressor cell ratio)*
606. Oehri M, Ninnis R, Girard J, Frey FJ, Keller U. Effects of growth hormone and IGF-I on glucocorticoid-induced protein catabolism in humans. Am J Physiol. 1996 Apr;270(4 Pt 1):E552-8. *(GH blocked the catabolic effects of glucocorticoids on protein metabolism)*
607. Grote FK, Van Suijlekom-Smit LW, Mul D, Hop WC, Ten Cate R, Oostdijk W, Van Luijk W, Jansen-van Wijngaarden CJ, De Muinck Keizer-Schrama SM. Growth hormone treatment in children with rheumatic disease, corticosteroid induced growth retardation, and osteopenia. Arch Dis Child. 2006 Jan;91(1):56-60. (increase in BMD for lumbar spine within the hGH group was significant.)

With vitamin D

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

With biphosphonates

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

With sodium floride

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

Exercise

616. Braith RW, Mills RM, Welsch MA, Keller JW, Pollock ML. Resistance exercise training restores bone mineral density in heart transplant recipients. J Am Coll Cardiol. 1996 Nov 15;28(6):1471-7 *(6 months of resistance exercise, consisting of low back exercise that isolates the lumbar spine and a regimen of variable resistance exercises, restores BMD toward pretransplantation levels.)*

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.*

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

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
622. **Deutschland:** Preventive, *Anti-aging* and Regenerative Medicine Master Program of the University of Dresden: http://www.di-uni.de/index.php?id=182
623. **Espana**: Máster en Medicina Antienvejecimiento y Longevidad of the Universitat Autónoma de Barcelona: http://www.il3.ub.edu/es/master/master-medicina-antienvejecimiento-longevidad.html_1489651066.html
624. **Malaysia**: Master of Science in Healthy Aging, Medical Aesthetic and Regenerative Medicine of the UCSI university (Kuala Lumpur: http://www.ucsiuniversity.edu.my/fomhs/programmes/postgraduate/MscAntiAging.aspx
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/#
626. **France** : Médecine morphologique et antiâge à l'Université de Paris-Descartes : http://www.scfc.parisdescartes.fr/index.php/descartes/formations/medecine/medecine-interne-medecine-generale/diu-medecine-morphologique-et-anti-age-image-corporelle-et-prevention-des-troubles-lies-a-l-avancee-en-age
627. **Brazil**: Post Graduation Lato Sensu Master of Science on Human Physiology au Talles de Mileto College (Sao Paulo) http://emec.mec.gov.br/emec/consulta-cadastro/detalhamento/d96957f455f6405d14c6542552b0f6eb/MTY5NDM=/93916316abe23148507bd4c260e4b878/MzE0NjE= (360h, 18 monthslong)

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

628. **Indonesia** (Bali) Udayana University in, "The anti-aging medicine [Masters] program: http://www.worldhealth.net/news/first_masters_program_in_anti-aging_medi
629. **Belgium** : Thérapeutiques anti-âge au Centre universitaire de Charleroi de 2001 à 2004 : http://www.thierrysouccar.com/blog/comment-trouver-un-medecin-anti-age

Not bound to university

630. **International/ Belgium:** Anti-aging medicine specialization of the World society of anti-aging medicine http://www.wosaam.ws

Placebo-controlled studies with recombinant human growth hormone: 507

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

631. Lewis AL, Jordan F, Patel T, Jeffery K, King G, Savage M, Shalet S, Illum L. Intranasal Human Growth Hormone (hGH) Induces IGF-1 Levels Comparable With Subcutaneous Injection With Lower Systemic Exposure to hGH in Healthy Volunteers. J Clin Endocrinol Metab. 2015 Nov;100(11):4364-71.
632. Keane J, Tajouri L, Gray B. The Effect of Growth Hormone Administration on the Regulation of Mitochondrial Apoptosis in-Vivo. Int J Mol Sci. 2015 Jun 5;16(6):12753-72.
633. Rasmussen MH, Olsen MW, Alifrangis L, Klim S, Suntum M. A reversible albumin-binding growth hormone derivative is well tolerated and possesses a potential once-weekly treatment profile. J Clin Endocrinol Metab. 2014 Oct;99(10):E1819-29
634. Tavares AB, Micmacher E, Biesek S, Assumpção R, Redorat R, Veloso U, Vaisman M, Farinatti PT, Conceição F. Effects of Growth Hormone Administration on Muscle Strength in Men over 50 Years Old. Int J Endocrinol. 2013;2013:942030.
635. Velloso CP, Aperghis M, Godfrey R, Blazevich AJ, Bartlett C, Cowan D, Holt RI, Bouloux P, Harridge SD, Goldspink G. The effects of two weeks of recombinant growth hormone administration on the response of IGF-I and N-terminal pro-peptide of collagen type III (P-III-NP) during a single bout of high resistance exercise in resistance trained young men. Growth Horm IGF Res. 2013 Jun;23(3):76-80.
636. Ramos SB, Brenu EW, Christy R, Gray B, McNaughton L, Tajouri L, Van Driel M, Marshall-Gradisnik SM. Assessment of immune function after short-term administration of recombinant human growth hormone in healthy young males. Eur J Appl Physiol. 2011 Jul;111(7):1307-12.
637. Rasmussen MH, Jensen L, Anderson TW, Klitgaard T, Madsen J. Multiple doses of pegylated long-acting growth hormone are well tolerated in healthy male volunteers and possess a potential once-weekly treatment profile. Clin Endocrinol (Oxf). 2010 Dec;73(6):769-76.
638. Meinhardt U, Nelson AE, Hansen JL, Birzniece V, Clifford D, Leung KC, Graham K, Ho KK. The effects of growth hormone on body composition and physical performance in recreational athletes: a randomized trial. Ann Intern Med. 2010 May 4;152(9):568-77.
639. Rasmussen MH, Bysted BV, Anderson TW, Klitgaard T, Madsen J. Pegylated long-acting human growth hormone is well-tolerated in healthy subjects and possesses a potential once-weekly pharmacokinetic and pharmacodynamic treatment profile. J Clin Endocrinol Metab. 2010 Jul;95(7):3411-7.
640. Nelson AE, Meinhardt U, Hansen JL, Walker IH, Stone G, Howe CJ, Leung KC, Seibel MJ, Baxter RC, Handelsman DJ, Kazlauskas R, Ho KK. Pharmacodynamics of growth hormone abuse biomarkers and the influence of gender and testosterone: a randomized double-blind placebo-controlled study in young recreational athletes. J Clin Endocrinol Metab. 2008 Jun;93(6):2213-22.
641. Erotokritou-Mulligan I, Bassett EE, Kniess A, Sönksen PH, Holt RI. Validation of the growth hormone (GH)-dependent marker method of detecting GH abuse in sport through the use of independent data sets. Growth Horm IGF Res. 2007 Oct;17(5):416-23. (2 independent double blind, placebo controlled, hGH administration studies)
642. Ehrnborg C, Ohlsson C, Mohan S, Bengtsson BA, Rosén T. Increased serum concentration of IGFBP-4 and IGFBP-5 in healthy adults during one month's treatment with supraphysiological doses of growth hormone. Growth Horm IGF Res. 2007 Jun;17(3):234-41.
643. Powrie JK, Bassett EE, Rosen T, Jørgensen JO, Napoli R, Sacca L, Christiansen JS, Bengtsson BA, Sönksen PH; GH-2000 Project Study Group. Detection of growth hormone abuse in sport. Growth Horm IGF Res. 2007 Jun;17(3):220-6.
644. Krag MB, Gormsen LC, Guo Z, Christiansen JS, Jensen MD, Nielsen S, Jørgensen JO. Growth hormone-induced insulin resistance is associated with increased intramyocellular triglyceride content but unaltered VLDL-triglyceride kinetics. Am J Physiol Endocrinol Metab. 2007 Mar;292(3):E920-7.
645. Giannoulis MG, Jackson N, Shojaee-Moradie F + Sonksen PH, Martin FC, Umpleby AM. Effects of growth hormone and/or testosterone on very low density lipoprotein apolipoprotein B100 kinetics and plasma lipids in healthy elderly men: a randomised controlled trial. Growth Horm IGF Res. 2006 Oct-Dec;16(5-6):308-17.
646. Chung L, Clifford D, Buckley M, Baxter RC. Novel biomarkers of human growth hormone action from serum proteomic profiling using protein chip mass spectrometry. J Clin Endocrinol Metab. 2006 Feb;91(2):671-7.
647. Healy ML, Gibney J, Pentecost C, Croos P, Russell-Jones DL, Sönksen PH, Umpleby AM. Effects of high-dose growth hormone on glucose and glycerol metabolism at rest and during exercise in endurance-trained athletes. J Clin Endocrinol Metab. 2006 Jan;91(1):320-7.
648. Ehrnborg C, Ellegård L, Bosaeus I, Bengtsson BA, Rosén T. Supraphysiological growth hormone: less fat, more extracellular fluid but uncertain effects on muscles in healthy, active young adults. Clin Endocrinol (Oxf). 2005 Apr;62(4):449-57.
649. Berggren A, Ehrnborg C, Rosén T, Ellegård L, Bengtsson BA, Caidahl K. Short-term administration of supraphysiological recombinant human growth hormone (GH) does not increase maximum endurance exercise capacity in healthy, active young men and women with normal GH-insulin-like growth factor I axes. J Clin Endocrinol Metab. 2005 Jun;90(6):3268-73.
650. Giannoulis MG, Boroujerdi MA, Powrie J, Dall R, Napoli R, Ehrnborg C, Pentecost C, Cittadini A, Jørgensen JO, Sonksen PH; GH-2000 Study Group. Gender differences in growth hormone response to exercise before

and after rhGH administration and the effect of rhGH on the hormone profile of fit normal adults. Clin Endocrinol (Oxf). 2005 Mar;62(3):315-22.
651. Yuen K, Frystyk J, Umpleby M, Fryklund L, Dunger D. Changes in free rather than total insulin-like growth factor-I enhance insulin sensitivity and suppress endogenous peak growth hormone (GH) release following short-term low-dose GH administration in young healthy adults. J Clin Endocrinol Metab. 2004 Aug;89(8):3956-64.
652. Hameed M, Lange KH, Andersen JL, Schjerling P, Kjaer M, Harridge SD, Goldspink G. The effect of recombinant human growth hormone and resistance training onIGF-I mRNA expression in the muscles of elderly men. J Physiol. 2004 Feb 15;555(Pt 1):231-40.
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Growth hormone therapy on growth hormone-deficient children: 46 placebo-controlled studies (50 with mixed studies)

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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)

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Obesity - children

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Surgery- children

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Edema disappears with GH dose reduction

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Viagra: first study and adverse events, including mortality and other

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

Healthy adults

Healthy young men

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

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

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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

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Aldosterone: 13 placebo-controlled trials – all in adults

Healthy men: IV aldosterone produces acute cardiovascular (sympathetic) effects (first 45 min after injection) and delayed (5 ½ - 6 ½ h after) increased vagal tone (parasymathetic predominance)

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

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

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Patients with disease

Orthostatic hypotension: Aldosterone reduces orthostatism

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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

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

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Orthostatic hypotension: Fludrocortisone significantly reduces orthostatic hypotension in patients

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

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

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

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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
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Borderline personality and major depressive disorders, healthy subjects: No effect of fludrocortisone on autobiographical memory
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Severe traumatic brain injury: Fludrocortisone associated to hydrocortisone at low doses does not significantly prevent hospital-acquired pneumonia
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Septic shock: Fludrocortisone associated to hydrocortisone at low doses produces beneficial effects, including better renal function
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Septic shock: Fludrocortisone associated to hydrocortisone at low doses reduces mortality
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Children

Children with syncope or severe presyncope: Fludrocortisone: produces significant beneficial effects to reduce syncopal symptoms; including syncope
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Thymosin alpha 1 treatment: 16 human placebo-controlled trials mentioned inPubmed

Elderly men: the immune stimuylation with thymosin-alpha-1 (1 trila, 85 patients)
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Chronic hepatitis C: the improvement with thymosin-alpha-1 (1 trial, 103 patients)
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Chronic hepatitis C: no significant improvement with thymosin-alpha-1 (1 trials, 571 patients)
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Cancer (overall) after radiotherapy or chemotherapy (immune depression): trend toward improvement with thymosin-alpha-1 or thymopentin (4trials, > 100 patients)
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Cancer (lung) after radiotherapy (immune depression): the improvement with thymosin-alpha-1 (2 trials, 63 patients))
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Senescence is associated with a decline of most hormone levels

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

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

Lower nocturnal serum melatonin and lower urinary melatonin metabolite with senescence

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

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Senescence is is associated with lower GH production

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a reduced amplitude and a phase advance

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

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

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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

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Senescence is associated with a decline in oxytocin secretion to stimuli

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Senescence is associated with a decline in oxytocin levels

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

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

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

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

Senescence is associated with an atrophy of the suprachiasmatic nuclei, which contain vasopressin-containing neurons

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

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Senescence is associated with no change in vasopressin levels in humans

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Senescence is associated with higher vasopressin levels in men

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Senescence is associated with decline in amplitude of the circadian cycle of serum vasopressin

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

Less vasopressin is additionally secreted in reaction to exercise

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

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

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

Decline or delay in vasopressin-induced renal concentrating ability

1202. Wilson PD, Dillingham MA. Age-associated decrease in vasopressin-induced renal water transport: a role for adenylate cyclase and G protein malfunction. Gerontology. 1992;38(6):315-21
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Decline in dilatation of brain arteries

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Decline in behavioral and cardiovascular responses

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Senescence is associated with a decline of the thyroid axis

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

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

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

1215. Kvetny J. Nuclear thyroxine and triiodothyronine binding in mononuclear cells in dependence of age. Horm Metab Res. 1985 Jan;17(1):35-8

Senescence is associated with alterations of the circadian cycle of serum TSH:

Lower amplitude and phase advance

1216. Greenspan SL, Klibanski A, Rowe JW, Elahi D. Age-related alterations in pulsatile secretion of TSH: role of dopaminergic regulation. Am J Physiol. 1991 Mar;260(3 Pt 1):E486-91
1217. Barreca T, Franceschini R, Messina V, Bottaro L, Rolandi E. 24-hour thyroid-stimulating hormone secretory pattern in elderly men. Gerontology. 1985;31(2):119-23

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

Senescence is associated with telomere shortening in parathyroid tissue

1218. Kammori M, Nakamura K, Kawahara M, Mimura Y, Kaminishi M, Takubo K. Telomere shortening with aging in human thyroid and parathyroid tissue. Exp Gerontol. 2002 Apr;37(4):513-21

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

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Senescence is associated with higher serum levels of Parathormone

1221. Vieth R, Ladak Y, Walfish 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
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Senescence is associated with a progressively (and excessively) higher secretion of parathyroid hormone in response to lower serum calcium levels

1226. Portale AA, Lonergan ET, Tanney DM, Halloran BP. Aging alters calcium regulation of serum concentration of parathyroid hormone in healthy men. Am J Physiol. 1997 Jan;272(1 Pt 1):E139-46

Senescence is associated with a need for progressively higher serum vitamin D3 levels and intake to reduce serum parathormone levels

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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

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

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

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

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

Senescence is associated with a decline in adrenal androgen levels

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The anabolic/catabolic hormone balance becomes increasingly inadequate with senescence

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Senescence is associated with alterations of the circadian cycle of serum DHEA sulphate:
a reduced amplitude up to a disappearance of the circadian rhythm

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

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

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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

1277. Khosla S, Melton LJ 3rd, Atkinson EJ, O'Fallon WM, Klee GG, Riggs BL. Relationship of serum sex steroid levels and bone turnover markers with bone mineral density in men and women: a key role for bioavailable estrogen. J Clin Endocrinol Metab. 1998 Jul;83(7):2266-74
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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

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Decrease of metabolic clearance of the estrogens with senescence

1284. Longcope C. Metabolic clearance and blood production rates of estrogens in postmenopausal women. Am J Obstet Gynecol. 1971 Nov;111(6):778-81

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

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Tubal ligation is associated with a decline of the ovarian-estrogen axis

1286. Rojansky N, Halbreich U. Prevalence and severity of premenstrual changes after tubal sterilization. J Reprod Med. 1991 Aug;36(8):551-5
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Senescence is associated with a decline of the adrenal- and ovarian-testosterone axes:

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

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Testosterone derives in women for more than 90% from the much quicker declining serum DHEA

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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*

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

Senescence in men is associated with a decline in testosterone levels

1295. Lam KS. Serum total and bioavailable testosterone levels, central obesity, and muscle strength changes with aging in healthy Chinese men. J Am Geriatr Soc. 2008 Jul;56(7):1286-91 *("The rates of decline in serum total testosterone and bioavailable testosterone levels were 0.2% and 1.14% per year")*
1296. 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")*
1297. 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
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Ostrowski S, Makaruk B. Sex hormones, HDL cholesterol and other lipoproteins in older males. Pol Merkur Lekarski. 2005 Mar;18(105):295-7
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1306. Tan MO, Karabiyik I, Uygur MC, Diker Y, Erol D. Serum concentrations of sex hormones in men with severe lower urinary tract symptoms and benign prostatic hyperplasia. Int Urol Nephrol. 2003;35(3):357-63
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1314. 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
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The speed of age-related decline of serum testosterone in men
1316. Vermeulen A. Plasma levels and secretion rate of steroids with anabolic activity in man. Environ Qual Saf Suppl. 1976;(5):171-80

Senescence in men is associated with a decline in metabolic clearance of testosterone
1317. Wang C, Catlin DH, Starcevic B, Leung A, DiStefano E, Lucas G, Hull L, Swerdloff RS. Testosterone metabolic clearance and production rates determined by stable isotope dilution/tandem mass spectrometry in normal men: influence of ethnicity and age. J Clin Endocrinol Metab. 2004 Jun;89(6):2936-41
1318. Baker HW, Burger HG, de Kretser DM, Hudson B, O'Connor S, Wang C, Mirovics A, Court J, Dunlop M, Rennie GC. Changes in the pituitary-testicular system with age. Clin Endocrinol (Oxf). 1976 Jul;5(4):349-72

Senescence in men is associated with alterations of the circadian cycle of serum testosterone levels: reduced amplitude and desynchronization of its circadian rhythm
1319. Bremner WJ, Vitiello MV, Prinz PN. Loss of circadian rhythmicity in blood testosterone levels with aging in normal men. J Clin Endocrinol Metab. 1983 Jun;56(6):1278-81

The age-related decline of serum testosterone starts in middle age in men
1320. Luboshitzky R, Shen-Orr Z, Herer P. Middle-aged men secrete less testosterone at night than young healthy men. J Clin Endocrinol Metab. 2003 Jul;88(7):3160-6

Senescence in men is associated with a loss of the circadian rhythm of serum testosterone
1321. Bremner WJ, Vitiello MV, Prinz PN. Loss of circadian rhythmicity in blood testosterone levels with aging in normal men. J Clin Endocrinol Metab. 1983;56:1278-81

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

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1323. Tan MO, Karabiyik I, Uygur MC, Diker Y, Erol D. Serum concentrations of sex hormones in men with severe lower urinary tract symptoms and benign prostatic hyperplasia. Int Urol Nephrol. 2003;35(3):357-63
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

1325. Liu PY, Takahashi PY, Roebuck PD, Iranmanesh A, Veldhuis JD. Aging in healthy men impairs recombinant human luteinizing hormone (LH)-stimulated testosterone secretion monitored under a two-day intravenous pulsatile LH clamp. J Clin Endocrinol Metab. 2005 Oct;90(10):5544-50

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

Reductions of progesterone levels with senescence in men

1326. Belanger A, Candas B, Dupont A, Cusan L, Diamond P, Gomez JL, Labrie F. Changes in serum concentrations of conjugated and unconjugated steroids in 40- to 80-year-old men. J Clin Endocrinol Metab. 1994 Oct;79(4):1086-90
1327. Tietz NW, Shuey DF, Wekstein DR. Laboratory values in fit aging individuals - sexagenarians through centenarians. Clin Chem. 1992 Jun;38(6):1167-85
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The progesterone increase after HCG stimulation disappears in elderly men

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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

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Decrease in handgrip strength

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Functional decline of the senses: from age 30 years on

1332. Backer GT and Martin GR. Molecular and biologic factors in aging: The origin, causes and prevention. Geriatric Medicine, 3rd ed., Springer, NY, 1997, p. 5

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

Hair grayness: start appearing from age 25 on

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Wrinkles¨ start appearing from age 25

1336. Tsukahara K, Fujimura T, Yoshida Y, Kitahara T, Hotta M, Moriwaki S, Witt PS, Simion FA, Takema Y. Comparison of age-related changes in wrinkling and sagging of the skin in Caucasian females and in Japanese females. J Cosmet Sci. 2004 Jul-Aug;55(4):351-71.

Wrinkles¨ start appearing from age 25 and **Pigment spots**: after age 40
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Sagging skin (after age 30)
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Sagging skin increases with age and **skin elasticity decreases with age**: after age 30
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Skin elasticity decreases with age: increases from age 30 on
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Skin elasticity decreases with age: increases from age 40 on
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Skeletal muscle mass: declines from age 25-30 (third decade) on
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Waist circumference: increases from age 25 on
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Body fat: increases from age 25 on
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Endocrine deficits after posttraumatic brain syndrome

Hypopituitarism in adults after traumatic brain injury
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Research Institute, Harbor-UCLA Medical Center, Torrance, California Division of Neurosurgery, UCLA School of Medicine
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Growth hormone deficiency after TBI

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GH, ACTH deficiencies after TBI

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GH, vasopressin and sexual hormone deficiencies after TBI

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Research Institute, Harbor-UCLA Medical Center, Torrance, California Division of Neurosurgery, UCLA School of Medicine
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GH, TSH, thyroid, ACTH and cortisol deficiencies after TBI

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Vasopressin, adrenal and thyroid deficiencies after TBI

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Adrenal deficiency after TBI

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Thyroid deficiencies after TBI

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Hypogonadism, low testosterone/low female hormones

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

Higher risk of obesity in people with premature gray hair

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

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

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

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

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

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

1394. Su LH, Chen LS, Lin SC, Chen HH. Association of androgenic alopecia with mortality from diabetes mellitus and heart disease. JAMA Dermatol. 2013 May;149(5):601-6

Higher risk of mortality in men with male pattern baldness

1395. Schnohr P, Nyboe J, Lange P, Jensen G. Longevity and gray hair, baldness, facial wrinkles, and arcus senilis in 13,000 men and women: the Copenhagen City Heart Study. J Gerontol A Biol Sci Med Sci. 1998 Sep;53(5):M347-50.

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

1397. Hawk E, Breslow RA, Graubard BI. Male pattern baldness and clinical prostate cancer in the epidemiologic follow-up of the first National Health and Nutrition Examination Survey. Cancer Epidemiol Biomarkers Prev. 2000 May;9(5):523-7 (Men with male pattern baldness prostate cancer: 50% Increased prostate cancer risk)
1398. Denmark-Wahnefried W, Schildkraut JM, Thompson D, Lesko SM, McIntyre L, Schwingl P, Paulson DF, Robertson CN, Anderson EE, Walther PJ. Early onset baldness and prostate cancer risk. Cancer Epidemiol Biomarkers Prev. 2000 Mar;9(3):325-8.

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

1399. Arias-Santiago S, Gutiérrez-Salmerón MT, Castellote-Caballero L, Buendía-Eisman A, Naranjo-Sintes R. Androgenic alopecia and cardiovascular risk factors in men and women: a comparative study. J Am Acad Dermatol. 2010 Sep;63(3):420-9.

Higher risk of dyslipidemia in women with female pattern baldness

1400. Esfandiarpour I, Hayatbatch MM, Abbassi, Moghaddam SD, Hosseininasab F. Evaluation of Lipid Profile in Women with Female Pattern Alopecia**.** Iran J Dermatol 2010;13: 78-81)

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

1401. Mansouri P, Mortazavi M, Eslami M, Mazinani M. Androgenic alopecia and coronary artery disease in women. Dermatol Online J. 2005 Dec 1;11(3):2.

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

1403. Haller U, Hepp H, Winter R. [Anti-aging or better aging: a contribution to the prevention of aging?]. Gynakol Geburtshilfliche Rundsch. 2003 Apr;43(2):69-70
1404. Lunenfeld B. Aging men--challenges ahead. Asian J Androl. 2001 Sep;3(3):161-8.

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

1405. Vahl N, Juul A, Jorgensen JO, Orskov H, Skakkebaek NE, Christiansen JS. Continuation of growth hormone (GH) replacement in GH-deficient patients during transition from childhood to adulthood: a two-year placebo-controlled study. J Clin Endocrinol Metab. 2000 May;85(5):1874-81(
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1407. Davies JS, Obuobie K, Smith J, Rees DA, Furlong A, Davies N, Evans LM, Scanlon MF. A therapeutic trial of growth hormone in hypopituitary adults and its influence upon continued prescription by general practitioners. Clin Endocrinol (Oxf). 2000 Mar;52(3):295-303

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

1408. Maaten JC, de Boer H, Kamp O, Stuurman L, van der Veen EA. Long-term effects of growth hormone (GH) replacement in men with childhood-onset GH deficiency. J Clin Endocrinol Metab. 1999 Jul;84(7):2373-80. (
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1410. Rudman D, Feller AG, Nagraj HS, Gergans GA, Lalitha PY, Goldberg AF, Schlenker RA, Cohn L, Rudman IW, Mattson DE. Effects of human growth hormone in men over 60 years old. N Engl J Med. 1990 Jul 5;323(1):1-6
1411. Olsovska V, Siprova H, Beranek M, Soska V. The influence of long-term growth hormone replacement therapy on body composition, bone tissue and some metabolic parameters in adults with growth hormone deficiency. Vnitr Lek. 2005 Dec;51(12):1356-64 (

Sarcopenia: the improvement with GH treatment

1412. Butterfield GE, Marcus R, Holloway L, Butterfield G. Clinical use of growth hormone in elderly people. J Reprod Fertil Suppl. 1993; 46:115-8
1413. Butterfield GE, Thompson J, Rennie MJ, Marcus R, Hintz RL, Hoffman AR. Effect of rhGH and rhIGF-1 treatment on protein utilization in elderly women. Am J Physiol. 1997 Jan; 272 (1 Pt 1): E 94-9
1414. Sartorio A, Narici MV. Growth hormone (GH) treatment in GH-deficient adults: effects on muscle size,strength and neural activation. Clin Physiol. 1994 Sep;14(5):527-37
1415. Janssen YJ, Doornbos J, Roelfsema F. Changes in muscle volume, strength, and bioenergetics during recombinant human ,growth hormone (GH) therapy in adults with GH deficiency. J Clin Endocrinol Metab. 1999 Jan;84(1):279-84
1416. Jorgensen JO, Pedersen SA, Thuesen L, Jorgensen J, Ingemann-Hansen T, Skakkebaek NE, Christiansen JS. Beneficial effects of growth hormone treatment in GH-deficient adults. Lancet. 1989 Jun 3;1(8649):1221-5

Physical appearance, body morphology improvement with GH treatment

1417. Hertoghe T. Growth hormone therapy in aging adults. Anti-aging Med Ther. 1997;1:10-28 (48 adults receiving 0first month 1 IU/day of growth hormone, then second and other months 0.5 IU/day , at follow-up study 2-6 months later: Sagging cheeks was the most frequent physical sign to improve (improved in 75.5% of complaining subjects), loose skinfolds under the skin (in 62.8%), sagging body silhouette (in 62.5%))
1418. Honda M, Yogi A, Ishizuka N, Genka I, Gatanaga H, Teruya K, Tachikawa N, Kikuchi Y, Oka S. Effectiveness of subcutaneous growth hormone in HIV-1 patients with moderate to severe facial lipoatrophy. Intern Med. 2007;46(7):359-62
1419. Zivicnjak M, Franke D, Ehrich JH, Filler G.Does growth hormone therapy harmonize distorted morphology and body composition in chronic renal failure? Pediatr Nephrol. 2000 Dec;15(3-4):229-35
1420. Eiholzer U, Schlumpf M, Nordmann Y, l'Allemand D. Early manifestations of Prader-Willi syndrome: influence of growth hormone. J Pediatr Endocrinol Metab 2001;14 Suppl 6:1441-4

GH therapy improves physical performance in adults

GH therapy: Improvement of exercise capacity and cardiac output

1421. Tritos NA, Danias PG. Growth hormone therapy in congestive heart failure due to left ventricular systolic dysfunction: a meta-analysis. Endocr Pract. 2008 Jan-Feb;14(1):40-9.
1422. Genth-Zotz S, Zotz R, Geil S, Voigtländer T, Meyer J, Darius H. Recombinant growth hormone therapy in patients with ischemic cardiomyopathy : effects on hemodynamics, left ventricular function, and cardiopulmonary exercise capacity. Circulation. 1999 Jan 5-12;99(1):18-21
1423. Fazio S, Sabatini D, Capaldo B, Vigorito C, Giordano A, Guida R, Pardo F, Biondi B, Saccà L. A preliminary study of growth hormone in the treatment of dilated cardiomyopathy. N Engl J Med. 1996 Mar 28;334(13):809-14.

GH therapy: Improvement of cardiac output

1424. Minczykowski A, Gryczynska M, Ziemnicka K, Czepczynski R, Sowinski J, Wysocki H. The influence of growth hormone (GH) therapy on cardiac performance in patients with childhood onset GH deficiency. Growth Horm IGF Res. 2005 Apr;15(2):156-64.

GH therapy: No improvement of cardiac output

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GH therapy: Improvement of muscular strength

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GH therapy improves mental performance in adults

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GH therapy improves the mood and sexuality in adults

Lower quality of life and fatigue: the improvement with GH treatment

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Depression: the improvement with GH treatment

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Loss of erectile function in animals: the improvement with GH treatment

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GH therapy reduces free radical levels

Free radical excess : significant decrease in oxidative stress

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GH therapy reduces the risk and/or severity of age-related diseases in adults

Hypercholesterolemia: the improvement with GH treatment

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Atherosclerosis: the improvement with GH treatment

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Heart failure and cardiac hypofunction: the improvement with GH treatment

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Obesity and visceral adiposity: the improvement with GH treatment in adults

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

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Osteoporosis: the improvement with long-term GH treatment

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

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Longevity: the association with higher IGF-1 levels

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

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Liver failure mortality: reduction with GH treatment

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

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

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Growth hormone receptor deficiency not associated with increased mortality

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Second part: Answer to critics

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