Anti-aging medicine, a science-based, essential medicine: Scientific references
La médecine anti-âge, une médecine scientifique, indispensable : Références scientifiques

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<th>Abstract</th>
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<td>Anti-aging medicine is booming. It enters more and more the universities. Its hormone and nutritional tests and therapies rely on numerous scientific studies, including double-blind placebo-controlled randomized studies. Its methods are often innovative to obtain more information or benefits with greater safety. The fundamental purpose of the anti-aging medicine is to optimize health and the quality of life, and through this, make the physical appearance more youthful.</td>
<td>La médecine anti-âge est en plein essor. Elle s'introduit de plus en plus dans les universités. Ses tests et thérapies hormonales et nutritionnelles s'appuient sur de nombreuses études scientifiques, dont des études randomisées en double aveugle contrôlées par placebo. Ses méthodes sont souvent novatrices, permettant d'obtenir plus d'informations ou de bénéfices avec une plus grande sécurité. Le but fondamental de la médecine anti-âge est d'optimiser la santé et la qualité de la vie, et par cela, rendre l'apparence physique plus jeune. Bien choisis et bien dosés ces traitements ne devraient pas augmenter le risque de maladies liées à l'âge comme le cancer et les maladies cardiovasculaires, mais au contraire le diminuer par le côté préventif des traitements. Les opposants à la médecine anti-âge ne réussissent pas à rassembler des arguments scientifiques valables et leur insistance à propager la persistance d'une société de petits vieux et vieilles plutôt que d’activement participer à rechercher des moyens pour atténuer le vieillissement est dommageable à tous ceux qui les suivent, à eux-mêmes en premier lieu.</td>
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Scientific references: Confronted with the abundance of scientific publications related to anti-aging medicine, we reduced their number in the official medical journal publication. You can download here the rest of the references on www.wosaam.ws, and for larger databanks purchase the corresponding textbooks or practical guide books on www.hertoghe.eu. Click on Books and find the Textbook of lifespan and anti-aging medicine, Textbook of nutrient therapy (of the World society of anti-aging medicine) and Hormone handbook (by Dr. Hertoghe). The small number of references in the original publication is marked by its number of order, in yellow underlined, in front of the reference, (1) e.g. for the first reference of the original article.) The references of overviews of the scientific literature on important hormone therapy issues are added and represented with a yellow background.


Anti-aging medicine: evidence based medicine//La médecine anti-âge : evidence based medicine

A society of sick and dependant older people or a society of healthy people ?
Une société de sujets âgés, malades et dépendants, ou une société de personnes en bonne santé ?

Plutôt prévenir que guérir

Facial wrinkles: the improvement with female hormone therapy
3. Schmidt JB, Binder M, Demschik G, Biegdmayer C, Reiner A. Treatment of skin aging with topical estrogens. Int J Dermatol. 1996 Sep;35(9):669-74 (“After treatment for 6 months with 0.01% estradiol and 0.3% estriol creams … the wrinkle depth and pore sizes had decreased by 61 to 100% in both groups. Furthermore, … the measurement of wrinkles using skin profilometry, revealed significant, or even highly significant, decreases of wrinkle depth in the estradiol and the estriol groups, respectively.”)


8. Phillips TJ, Symons J, Menon S; HT Study Group. Does hormone therapy improve age-related skin changes in postmenopausal women? A randomized, double-blind, double-dummy, placebo-controlled multicenter study assessing the effects of norethindrone acetate and ethinyl estradiol in the improvement of mild to moderate age-related skin changes in postmenopausal women. J Am Acad Dermatol. 2008 Sep;59(3):397-404.e3. (“Low-dose hormone therapy for 48 weeks in postmenopausal women did not significantly alter mild to moderate age-related facial skin changes. … there were slight decreases in all parameters for all treatment groups for the primary subject end points, but there were no statistically significant differences between the N/A/EE groups and placebo”)


10. Holzer G, Riegler E, Höngismann H, Farokhnia S, Schmidt JB. Effects and side-effects of 2% progesterone cream on the skin of peri- and postmenopausal women: results from a double-blind, vehicle-controlled, randomized study. Br J Dermatol. 2005 Sep;153(3):626-34 (“16 weeks of topical 2% progesterone in peri- and postmenopausal women provided “significant increase of the elastic skin properties, … greater reduction in wrinkle counts (29.10% vs. 16.50%) and wrinkle depth (9.72% vs. 7.35%) around the right eye, a greater decrease in nasolabial wrinkle depth (9.72% vs. 6.62%) and a significantly higher (P < 0.05) increase in skin firmness (23.61)” compared to control cream.”

**Facial wrinkles, sagging cheeks: the improvement with growth hormone therapy**

11. Hertoghe T. Growth hormone therapy in aging adults. Anti-Aging Medical Therapeutics (Eds Klatz RM & Goldman R - Chicago) 1997:1:10-28 (Study with 48 patients aged 27 to 82 years, mean age 51 years 6 months …in each participant a treatment trial was started at an average dose of 0.75 IU or 0.25 mg per day during tow to three months. 18 physical signs and 12 symptoms suggestive of growth hormone deficiency were investigated by answers of the patient to a questionnaire. Most signs and symptoms improved in the patients. Improvement in physical signs was achieved 75.5 % to 9.5 % of complaining patients depending on the sign. Improvement in symptoms reached between 86.8% to 71% of the patients on growth hormone for all twelve symptoms. Sagging cheeks, a wrinkled face and pouches under the eyes were the main physical signs to regress. Permanent fatigue, easy exhaustion with physical activity, and poor resistance to stress were the three major symptoms to regress.)

**Facial wrinkles, rigid skin: the improvement with DHEA therapy**

12. Nouveau S, Bastien P, Baldo F, de Lacharriere O. Effects of topical DHEA on aging skin: a pilot study. Maturitas. 2008 Feb 20;59(2):174-81 (“DHEA treatment increased .. sebum” secretion, “tends to improve skin brightness, to counteract paper appearance of skin and epidermal atrophy,could also act on skin process related to wrinkles, but this result remains to be confirmed”)

13. El-Alfy M, Deloche C, Azzi L, Bernard BA, Bernerd F; Coutet J, Chauussade V, Martel C, Leclaire J, Labrie F. Skin responses to topical dehydroepiandrosterone: implications in anti-ageing treatment? Br J Dermatol. 2010 2010 Nov;163(5):986-76 (“DHEA cream on the face, arms, back of hands, upper chest and right thigh … markedly increased .. androgen receptor expression, procollagen 1 and 3 mRNAs and heat shock protein (HSP47), a molecule believed to have chaperone-like functions potentially affecting procollagen biosynthesis … topical DHEA could be used as an efficient and physiological anti-ageing skin agent.”)

**Atherosclerosis: the improvement with GH treatment**
Atherosclerosis: the improvement with meditation

Atherosclerosis: the improvement with female hormone therapy

We are all born with hormone deficiencies//Nous sommes tous nés avec des carences hormonales

Pollutants that affect the endocrine system of newborns

Progressive increase in hormone deficiencies with age, which may cause senescence

Numerous intermediate degrees of hormone deficiency exist, as abundant as eye(sight) problems
Il existe de nombreux degrés intermédiaires de carence hormonale, aussi abondants que les troubles de la vue

Hormone therapies are essential for health maintenance
Les thérapies hormonales sont essentielles au maintien de la bonne santé

Bowed back: the improvement with growth hormone therapy
Loose muscles: the improvement with testosterone therapy


Diminished cardiac output: the improvement with growth hormone therapy


Hypercholesterolemia: the improvement with thyroid treatment


Hormone reference values are statistical references and not limits between health and disease
Les valeurs de références hormonales sont des valeurs statistiques et non pas des limites entre santé et maladie


Lower estrogen levels: association with higher disease risks


Frequent hormone deficits at blood levels within the reference range
Les déficits hormonaux sont nombreux à des taux sanguins à l’intérieur de l’intervalle de référence

Higher coronary heart disease mortality: association with serum TSH within the reference range

SERUM TSH: IS THE TSH SERUM MEASUREMENT ALONE SUFFICIENT FOR DIAGNOSIS AND FOLLOW-UP OF THYROID DEFICIENCY?

Claim: TSH is the first line test to do. It is sufficient to diagnose all forms of eu-, hypo- and hyperthyroidism. No other test is necessary for the diagnosis.

Facts: TSH is often insufficient on its own to diagnose between eu-, hypo- and hyperthyroidism, particularly to diagnose milder, borderline states of hypothyroidism. Other tests are necessary, as is a complete clinical evaluation (medical history, actual complaints, physical examination) of the patient.

Article defending the serum TSH test as the first line approach to diagnose thyroid dysfunction

Doubts on the usefulness of the serum TSH test alone for diagnosis
Overreliance on laboratory tests without clinical evaluation may lead to considerable diagnostic errors
4. Becker DV, Bigos ST, Gaitan E, Morris JCrd, rallison ML, Spencer CA, Sugarawa M, Van Middlesworth L, Wartofsky L. Optimal use of blood tests for assessment of thyroid function. JAMA 1993 Jun 2; 269: 273 (“the decision to initiate therapy should be based on both clinical and laboratory findings and not solely on the results of a single laboratory test”)

Discussions and controversy in medical associations and journals on the TSH reference range
6. Surks MI, Ortiz E, Daniels GH, Sawin CT, Col NF, Cobin RH, Frankshon JM, Burman KD, Denke MA, Gorman C, Cooper RS, Weissman NJ. Subclinical thyroid disease: scientific review and guidelines for diagnosis and management. JAMA. 2004;291:228–38 (conclusions of a consensus panel of the American Thyroid Association, and American Association of Clinical Endocrinology. Although the panel concluded that there was good data that patients with slight elevations of TSH above 4.5 may progress to overt hypothyroidism, and that levothyroxine therapy would prevent symptoms, they did not agree that early treatment provided any benefit!)
8. Wartofsky L, Dickey RA. The evidence for a narrower thyrotropin reference range is compelling. J Clin Endocrinol Metab. 2005 Sep;90(9):5483-8 (remarkable article of which a lot of the following information is extracted)
11. Ringel MD, Mazzaferrri EL. Editorial: subclinical thyroid dysfunction: can there be a consensus about the consensus? J Clin Endocrinol Metab. 2005:90:588–90
12. Pinchera A. Subclinical thyroid disease: to treat or not to treat? Thyroid. 2005;15:1–2

Studies that show that the serum TSH reference range of 0.1-5.1 mU/liter for a POPULATION is too large

Studies indicating a population mean value of 1.5 mU/liter for an iodine-sufficient population
A longitudinal study in diabetics where a baseline TSH levels above the 1.53 mU/liter predicted subsequent thyroid dysfunction, whereas no thyroid dysfunction if TSH levels < 1.53 mU/liter, the reference range for diabetics should then be 0.4–1.52 mU/liter

When data for subjects with positive TPOAb or a family history of autoimmune thyroid disease are excluded, the normal reference interval becomes much tighter, i.e. 0.4–2.0 mU/liter. This tighter reference range may certainly be more applicable to African-Americans, who have a lower mean TSH


Publications with data to support a more narrow reference range for serum TSH that would be obtained when persons with diffuse hypoechochogenicity of the thyroid on ultrasound, a condition that precedes thyroid peroxidase antibody positivity in autoimmune thyroid disease, would be excluded


For the American Association of Clinical Endocrinologists the revised reference TSH range is 0.3–3.0 mU/L

Ethnic differences: the mean TSH level in African-Americans is 1.18 mU/liter, in contrast to a mean of 1.40 mU/liter in Caucasians, due to the greater frequency of autoimmune thyroid disease in whites (12.3%) than in blacks (4.3%), which may have unjustifiedly skewed the upper end of the TSH curve (NHANES data). For African-Americans, the TSH reference range should therefore be lower than in whites

In 2003, the National Academy of Clinical Biochemistry (NACB) has reduced the upper limit of the reference range from 5.5 to 4.1 mU/L, but stating also that "greater than 95% of healthy, euthyroid subjects have a serum TSH concentration between 0.4 - 2.5 mU/L." Patients with a serum TSH >2.5 mU/L, when confirmed by repeat TSH measurement made after 3 to 4 weeks, may be in the early stages of thyroid failure, especially if thyroid peroxidase antibodies are detected.

Supporters of the recommendations of the consensus panel (Endocrine Society, American Association of Clinical Endocrinologists, American Thyroid Association) promote a target TSH range of 1.0–1.5 mU/liter in patients already receiving T4 therapy.

The lower end of the normal or reference range for TSH lies between 0.2 and 0.4 mU/liter, as indicated by a number of clinical studies:

- Hershman JM, Pekary AE, Berg L, Solomon DH, Sawin CT. Serum thyrotropin and thyroid hormone levels in elderly and middle-aged euthyroid persons. J Am Geriatr Soc. 1993;41:823–8

The TSH reference range for an individual is narrower than the reference range for a population.

The value of a population-based reference range is limited when the individual patient-based reference range (i.e. his personal reference range) is narrow.

- Harris EK. Effects of intra- and interindividual variation on the appropriate use of normal ranges. Clin Chem. 1974;20:1535–42

The individual TSH reference ranges are remarkably narrow within a relatively small segment of the population reference range, i.e. confined to only 25% of a range of 0.3–5.0 mU/liter.

A shift in the TSH value of the individual outside of his or her individual reference range, but still within the population reference range, would not be normal for that individual. For example, an individual (as in Anderson’s series) with a personal range of 0.5–1.0 mU/liter would be at subphysiological thyroid hormone levels at the population mean TSH of 1.5 mU/liter (as explained by Wartofsky 2005).

- Andersen S, Petersen KM, Brunn NH, Laurberg P. Narrow individual variations in serum T4 and T3 in normal subjects: a clue to the understanding of subclinical thyroid disease. J Clin Endocrinol Metab. 2002;87:1068–72
Studies of twins have data to support that each of us has a genetically determined optimal free T4 (FT4)-TSH set point or relationship


A measured TSH difference of 0.75 mU/liter can already be significant in a patient. The NACB guideline 8 states that “the magnitude of difference in ...TSH values that would be clinically significant when monitoring a patient’s response to therapy... is 0.75 mU/liter.” Greater TSH fluctuations in a specific patient may mean that s/he becomes hypothyroid or hyperthyroid.


A serum TSH that rises in a given individual from a set point of 1.0 to 3.5 is likely to be abnormally elevated and imply early thyroid failure. A minor change in serum free T4 results in an amplified change in TSH to outside of the usual population-based reference range, although the free T4 is still within its own population-based reference range, because of the the log-linear relationship between TSH and free T4. In the case of subclinical hypothyroidism, for example, a slight drop in free T4 results in an amplified and inverse response in TSH secretion (as explained by Wartofsky 2005)


There is a 3-fold difference between the average daily maximal TSH (3) and minimal TSH (1 mIU/ml)


Conclusion: TSH reference range is too large => need for narrower ranges


47. Dickey RA, Wartofsky L, Feld S. Optimal thyrotropin level: normal ranges and reference intervals are not equivalent. Thyroid. 2005 Sep;15(9):1035-9

48. Wartofsky L, Dickey RA. The evidence for a narrower thyrotropin reference range is compelling. J Clin Endocrinol Metab. 2005 Sep;90(9):5483-8

Other arguments that may explain why the TSH test alone is not the only test

The TSH test is insufficient to diagnose all forms of hypothyroidism, including the borderline forms.

The frequency of abnormal TSH values


The pituitary 5'-deiodinase type 2 that converts thyroxine into triiodothyronine (T3), is different than the liver and kidney 5'-deiodinase type 1 that provides the T3 for the rest of the body. This difference may explain why TSH secretion and thus serum TSH secreted by the pituitary gland may be normal, while the rest of the body may be in a thyroid deficient state.


In fasting, hypothyroidism or selenium deficiency for example, the 5'-deiodinase of the pituitary gland increases or remains unchanged, while that of the liver decreases.


A normal or low serum TSH may reflect in elderly persons hypothyroidism in peripheral tissues, and not anymore eu- or hyperthyroidism, because the pituitary gland has aged. Progressively with increasing age, the serum TSH test becomes less reliable as a diagnostic test.

Necessity for other tests than the TSH to diagnosis thyroid dysfunction, e.g. the serum free T4

Ladenson PW. Diagnosis of hypothyroidism. In Werner and Ingbar's The Thyroid, 7th edition, Braverman LE and Utiger RE, Lippincott-Raven Publishers, Philadelphia. 1996; 878-82

Need to analyse valuable indicators of peripheral activity such as the serum levels of plasma binding proteins SHBG, TBG, CBG, or of thyroid-dependent enzymes such as alkaline phosphatase, osteocalcin


Aging


**Fasting**

69. Croxson MS, Hall TD, Kletzky OA, Jaramillo JE, Nicoloff OA. Decreased serum thyrotropin induced by fasting. J Clin Endocrinol Metab. 1977; 45: 560


**Strenuous physical exercise**

73. Scanlon MF, Toft AD. Regulation of thyrotropin secretion. In Werner and Ingbar's The Thyroid, 7th edition

**Pregnancy (first trimester)**


**Depression and anxiety disorders**


**Non-thyroidal diseases:** diabetes mellitus, Cushing’s syndrome, renal failure, cancer, myocardial infarction, AIDS, post-traumatic syndromes, chronic alcoholic liver disease, other illnesses


**Medications:**
- Thyroid therapy, estroprogestative birth control pills, progestogens, anti-inflammatory agents (incl. glucocorticoids and aspirin), antidepressants, L-Dopa, bromocriptine, neuroleptica, anti-hypertensives, antiarrhythmics (amiodarone), hypolipemic agents, IGF, somatostatin, etc.

101. Chopra U, Carlson HE, Solomon DH. Comparison of inhibitory effects of 3,5,3'-triiodothyronine (T3), thyroxine (T4), 3,3',5'-triiodothyronine (rT3), and 3,3'-diodothyronine (T2) on thyrotropin-releasing hormone-induced release of thyrotropin in the rat in vitro. Endocrinology. 1978; 103(2): 393-402


Toxic foods: MSG, alcohol


Thyroid diseases: hyperthyroidism, Graves-Basedow disease, nodular goiter, thyroiditis, secondary or tertiary hypothyroidism, congenital hypothyroidism


FACTORS that ELEVATE the serum TSH

Neonatus, stress - emotional arousal, cold exposure, sleep deprivation, adrenal insufficiency, recovery from severe illness, congenital malformations


Medications: iodine, antithyroida, lithium, neuroleptica (haloperidol, chlorpromazine), cimetidine, sulfapyridine, clomifen, antidepressants (sertraline), antihistaminic agents, cholestrogaphic agents, etc.


Autoimmune thyroiditis and hypothyroidism: primary, iodine-deficient, thyroid hormone resistance


TSH-secreting tumors (rare)


Factors that elevate or depress serum TSH

Physiological serum TSH fluctuations


Variations in the biological activity of TSH


100. Hiromoto M, Nishikawa M, Ishihara T, Yoshikawa N, Yoshimura M, Inada M. Bioactivity of thyrotropin (TSH) in patients with central hypothyroidism: Comparison between the in vivo 3,5,3'-triiodothyronine response to TSH and in vitro bioactivity of TSH. J Clin Endocrinol Metab. 1995 Apr;80(4):1124-8

TSH test kit imperfections


105. Laurberg P. Persistent problems with the specificity of immunometric TSH assays. Thyroid. 1993 Winter;3(4):279-83


115. Ealey PA, Marshall NJ, Ekins RP. Time-related thyroid stimulation by thyrotropin and thyroid-stimulating antibodies, as measured by the cytochemical section bioassay. J Clin Endocrinol Metab. 1981;52(3): 483-7

Doubts on the adequateness of measuring the serum TSH as a help to monitor a thyroid treatment ( follow-up)

The serum TSH test for follow-up: The risk of misinterpretation increases when monitoring the treatment of hyper- or hypothyroidism


In 36-47 % of clinically euthyroid patients receiving adequate long-term thyroid therapy for hypothyroidism, an undetectable serum TSH is found

117. Franklin JA, Black EG, Betteridge J, Sheppard MC. Comparison of second and third generation methods for measurement of serum thyrotropin in patients with overt hyperthyroidism, patients receiving thyroxine therapy, and those with nonthyroidal illness, J Clin Endocrinol Metab 1994; 78(6): 1368-71


After intake of thyroid hormones, the serum TSH is transitorily depressed within 60 minutes and remains low for up to 9 hours after intake

119. Chopra U, Carlson HE, Solomon DH. Comparison of inhibitory effects of 3,5,3'-triiodothyronine (T3), thyroxine (T4), 3,3',5'-triiodothyronine (rT3), and 3,3'-diiodothyronine (T2) on thyrotropin-releasing hormone-induced release of thyrotropin in the rat in vitro. Endocrinology. 1978;103(2):393-402
Some patients who exhibit reversion of an initially high TSH level back into the reference range, are found to subsequently develop mild thyroid failure

Supporters of the recommendations of the consensus panel promote a target TSH range of 1.0–1.5 mU/liter in patients already receiving T4 therapy, whereas they refuse to accept TSH levels of 3–10 mU/liter as abnormal in patients not receiving T4 therapy.

The lower end of the normal or reference range for TSH lies between 0.2 and 0.4 mU/liter, as indicated by a number of clinical studies

Other tests: urinary T3 as a complementary test

Evidence suggests that not all TSH levels within the reference ranges are healthy; some may be indicative of mild thyroid failure, and thus require correction with thyroid replacement.
Studies with data that indicate that

1) The healthiest serum TSH levels may be found in the lower three quartiles of the reference range

Study with suggestion that a healthy serum TSH should be in the lower three quartiles (lower 75%) of the reference range in patients with major depression, as serum TSH levels in the upper 25th percentile of the normal reference range may be associated with characteristics of a more severe form of depression such as recurrent depression (with severe major depressive episodes), presence of somatic disease condition, suicide attempts, etc.


Study with suggestion that a healthy serum TSH should be in the lower three quartiles (lower 75%) of the reference range in depressed hospitalized patients, otherwise, in case of a serum TSH level in the upper quartile (25%) of the reference range, there may be an increased risk of more severe form of depression and slower or impaired response to antidepressant therapy


2) The healthiest serum TSH levels may be found below the 3 mU/L

Study with suggestion that a healthy serum TSH should be below 3 mU/l in patients with autoimmune thyroiditis, otherwise cardiac abnormalities may be found found at Doppler imaging


Study with suggestion that a healthy serum TSH should be below 3 mU/l in post-partum women, otherwise the risk of having had post-partum hypothyroidism and development of recurrent hypothyroidism after treatment withdrawal in the future is high

4. Azizi F. Age as a predictor of recurrent hypothyroidism in patients with post-partum thyroid dysfunction. J Endocrinol Invest. 2004 Dec;27(11):996-1002. Endocrine Research Center, Shaheed Beheshti University of Medical Sciences, Tehran, IR Iran

3) The healthiest serum TSH levels may be found in the lower half of the reference range

Study with suggestion that a healthy serum TSH should be equal to or below 2.5 mIU/l in pregnant women, or otherwise there may be a significantly increased risk of auto-immune thyroid disease (positive for anti-thyroid peroxidase antibodies), which itself is associated with an increased risk of overt hypothyroidism. The risk increased with age.


Study with suggestion that a healthy serum TSH should be equal to or below 2.5 mIU/l in women undergoing in vitro fertilization, or otherwise there may be an increased risk of a lower gestational age at delivery and lower birth weight of the baby

**Study with suggestion that a healthy serum TSH should be equal to or below 2 for pregnant women, otherwise in case their serum TSH is above 2, the risk to deliver a low birth weight (< 2.5 kg) baby may double**


**Study with suggestion that a healthy serum TSH should be equal to or below 1.9 for pregnant women, otherwise there may be an increased risk of auto-immune thyroiditis**


**Study with suggestion that a healthy serum TSH should be below 2.1 mU/l in angina patients, or otherwise serum creatinine, Gensini’s score (assigns a severity score for a stenosed vessel depending on the degree of luminal narrowing and the importance of its location), and the incidence of multiple vessel disease, may be higher**

9. Yun KH, Jeong MH, Oh SK, Lee EM, Lee J, Rhee SJ, Yoo NJ, Kim NH, Ahn YK, Jeong JW. Relationship of thyroid stimulating hormone with coronary atherosclerosis in angina patients. Int J Cardiol. 2007 Jan 11; [Epub ahead of print] Department of Cardiovascular Medicine, Wonkwang University Hospital, Iksan, South Korea

**Study with suggestion that a healthy serum TSH should be equal or below 2 mU/l in patients taking L-thyroxine-replacement therapy, or otherwise higher serum homocysteine and CRP levels may be found**

10. Gursoy A, Ozduman Cin M, Kamel N, Gullu S. Which thyroid-stimulating hormone level should be sought in hypothyroid patients under L-thyroxine replacement therapy? Int J Clin Pract. 2006 Jun;60(6):655-9. Department of Endocrinology and Metabolic Diseases, Ankara University, School of Medicine, Ankara, Turkey. alptekingursoy@hotmail.com

**Study with suggestion that a healthy serum TSH should be below 2.01 in normal individuals, or otherwise mild increases of arterial stiffness may occur**

11. Dagre AG, Lekakis JP, Papaioannou TG, Papamichael CM, Koutras DA, Stamatelopoulos SF, Alevizaki M. Arterial stiffness is increased in subjects with hypothyroidism. Int J Cardiol. 2005 Aug 3;103(1):1-6 Vascular Laboratory, Department of Clinical Therapeutics, Alexandria University Hospital, Athens, Greece

**Study with suggestion that a healthy serum TSH should be below 2 mU/l in normotensives, otherwise the risk of familial predisposition to hypertension and thus the risk of hypertension may be increased**


**Study with suggestion that a healthy serum TSH should be below 2 mU/l in patients with auto-immune thyroid antibodies, otherwise the patients may develop hypercholesterolemia (high total cholesterol >7.5 mmol/l and a high LDL cholesterol) that can be significantly reduced by two months of a small dose of 50 µg/day thyroxine**

13. Michalopoulou G, Alevizaki M, Piperingos G, Mitsibounas D, Mantzos E, Adamopoulos P, Koutras DA. High serum cholesterol levels in persons with 'high-normal' TSH levels: should one extend the definition of subclinical
Study with suggestion that a healthy serum TSH should be below 1.98 mU/L in patients with coronary artery disease, otherwise the risk of aggravation of coronary heart disease may be higher

14. Auer J, Berent R, Weber T, Lassnig E, Eber B. Thyroid function is associated with presence and severity of coronary atherosclerosis. Clin Cardiol. 2003 Dec;26(12):569-73. Second Medical Department, Division of Cardiology and Intensive Care, General Hospital Wels, Wels, Austria. johann.auer@khwels.at

Study with suggestion that a healthy serum TSH should be below 2 mU/l in patients with auto-immune thyroiditis, or otherwise there is an increased risk of upcoming overt hypothyroidism


4) The healthiest serum TSH levels may be found in the lower tertile (33%) of the reference range

Study with suggestion that a healthy serum TSH should be /equal to or below 1.53 mU/L diabetic patients, otherwise, if the TSH is higher, the risk may highly increase of developing overt hypothyroidism in the next years


5) The healthiest serum TSH levels may be found in the lower quartile (lower 25%) of the reference range

Study with suggestion that a healthy serum TSH should be /in the lower quartile of the reference range in normal individuals, otherwise, if the TSH is higher, and in particular if the TSH in the upper 25% of the reference range, the risk may increase of having a greater increase in body mass index over 7 years

17. Nymes A, Jorde R, Sundsfjord J. Serum TSH is positively associated with BMI. Int J Obes (Lond). 2006 Jan;30(1):100-5 Department of Geriatric Medicine, University Hospital of North Norway, Tromso. audhild.nymes@unn.no

Study with suggestion that a healthy serum TSH should be in the lower quartile ((25%) of the reference range in adult women, otherwise, if the TSH is higher, and in particular if the TSH in the upper 25% of the reference range, the risk may increase of having cardiovascular abnormalities such as increased waist circumference, body mass index (BMI), glucose, triglyceride, and systolic blood pressure.


Study with suggestion that a healthy serum TSH should be in the lower quartile of the reference range in normal individuals, otherwise, if the TSH is higher, and in particular if the TSH is in the upper 25% of the reference range, the risk may increase of having higher systolic and diastolic blood pressures. Optimally, is to have a serum TSH below the 1.88 in males and 1.79 in females

Study with suggestion that a healthy serum TSH should be below 0.4 mU/L in patients with palpable thyroid enlargement, otherwise the risk of thyroid malignancy may increase in parallel with the serum TSH level.

20. Boelaert K, Horacek J, Holder RL, Watkinson JC, Sheppard MC, Franklyn JA. Serum thyrotropin concentration as a novel predictor of malignancy in thyroid nodules investigated by fine-needle aspiration. J Clin Endocrinol Metab. 2006 Nov;91(11):4295-301. Division of Medical Sciences, University of Birmingham, Edgbaston, Birmingham B15 2TH, United Kingdom. k.boelaert@bham.ac.uk

Study with suggestion that a healthy serum TSH should be below 0.4 mU/L in patients with palpable thyroid enlargement, otherwise, at levels of serum TSH above the 0.4 mU/L, the risk of thyroid malignancy may increase.

21. Kumar H, Daykin J, Holder R, Watkinson JC, Sheppard MC, Franklyn JA. Gender, clinical findings, and serum thyrotropin measurements in the prediction of thyroid neoplasia in 1005 patients presenting with thyroid enlargement and investigated by fine-needle aspiration cytology. Thyroid. 1999 Nov;9(11):1105-9. Department of Medicine, University of Birmingham, Queen Elizabeth Hospital, Edgbaston, United Kingdom

6) The healthiest serum TSH levels may be found in the lower quintile (lower 20%) of the reference range

Study with suggestion that a healthy serum TSH should be below 0.4 mU/L, otherwise the BMI (body mass index) is increasingly higher, above the 24.6.


7) Adverse associations between serum TSH within the reference range and pathological parameters

Study with suggestion that a higher serum TSH levels within the reference range may be associated with increased dyslipidemia in normal individuals without known thyroid disease: increases in total serum cholesterol, LDL cholesterol, non-HDL cholesterol & and in particular triglycerides, and a (linear) decrease in HDL cholesterol (with increasing TSH) (*Significant association of serum TSH with lipid parameters* The risk further increases in men over age 50 and overweight individuals.)

23. Asvold BO, Vatten LJ, Nilsen TI, Bjoro T. The association between TSH within the reference range and serum lipid concentrations in a population-based study. The HUNT Study. Eur J Endocrinol. 2007 Feb;156(2):181-6. Department of Public Health, Faculty of Medicine, Norwegian University of Science and Technology, N-7489 Trondheim, Norway

Study with suggestion that higher serum TSH levels within the reference range in patients with insulin resistance may be associated with linear increases in LDL cholesterol and reductions in HDL cholesterol (with increasing serum TSH levels above 1.5 MU/l)


Study with suggestion that higher serum TSH levels within the reference range in men may be associated with increased prostate cancer risk

25. Lehrer S, Diamond EJ, Stone NN, Stock RG. Serum thyroid-stimulating hormone is elevated in men with Gleason 8 prostate cancer. BJU Int. 2005 Aug;96(3):328-9. Department of Radiation Oncology, Mount Sinai Medical Center, Bronx, New York, NY 10029, USA. stevenlehr@hotmail.com

Study with suggestion that higher serum TSH levels within the reference range in women may be associated with increased breast cancer risk (*positive association of serum TSH with breast cancer risk*)


30. Andersen S, Petersen KM, Brunn NH, Laurberg P. Narrow individual variations in serum T4 and T3 in normal subjects: a clue to the understanding of subclinical thyroid disease. J Clin Endocrinol Metab. 2002;87:1068–72


35. Ayala A; Wartofsky L. Minimally symptomatic (subclinical) hypothyroidism. Endocrinologist. 1997;7:44–50

36. Studies that show for each individual the reference range for thyroid tests is different in particular for serum TSH, and constitutes a smaller part of the population reference range presented by the laboratory.

The TSH reference range for an INDIVIDUAL is narrower than the reference range for a population.

27. The value of a population-based reference range is limited when the individual patient-based reference range (i.e. his personal reference range) is narrow.


The individual TSH reference ranges are remarkably narrow within a relatively small segment of the population reference range, i.e. confined to only 25% of a range of 0.3–5.0 mU/liter. A shift in the TSH value of the individual outside of his or her individual reference range, but still within the population reference range, would not be normal for that individual. For example, an individual (as in Anderson’s series) with a personal range of 0.5–1.0 mU/liter would be at subphysiological thyroid hormone levels at the population mean TSH of 1.5 mU/liter (as explained by Wartofsky 2005)

30. Andersen S, Petersen KM, Brunn NH, Laurberg P. Narrow individual variations in serum T4 and T3 in normal subjects: a clue to the understanding of subclinical thyroid disease. J Clin Endocrinol Metab. 2002;87:1068–72

Studies of twins have data to support that each of us has a genetically determined optimal free T4 (FT4)-TSH set point or relationship.


A measured TSH difference of 0.75 mU/liter can already be significant in a patient. The NACB guideline 8 states that “the magnitude of difference in ... TSH values that would be clinically significant when monitoring a patient’s response to therapy... is 0.75 mU/liter.” Greater TSH fluctuations in a specific patient may mean that s/he becomes hypothyroid or hyperthyroid.


A serum TSH that rises in a given individual from a set point of 1.0 to 3.5 is likely to be abnormally elevated and imply early thyroid failure. A minor change in serum free T4 results in an amplified change in TSH to outside of the usual population-based reference range, although the free T4 is still within its own population-based reference range, because of the the log-linear relationship between TSH and free T4. In the case of subclinical hypothyroidism, for example, a slight drop in free T4 results in an amplified and inverse response in TSH secretion (as explained by Wartofsky 2005)


35. Ayala A; Wartofsky L. Minimally symptomatic (subclinical) hypothyroidism. Endocrinologist. 1997;7:44–50

There is a 3-fold difference between the average daily maximal TSH (3) and minimal TSH (1 mIU/ml)
4. Publications on the need for narrower reference ranges for the thyroid tests:


5. Excessive fluctuations of serum levels of TSH

41. Brabant G, Prank K, Ranft U, Schuermeyer T, Wagner TO, Hauser H, Kummer B, Feistner H, Hesch RD, von zur Mühlen A. Physiological regulation of circadian and pulsatile thyrotropin secretion in normal man and woman. J Clin Endocrinol Metab. 1990 Feb;70(2):403-9. (There is a 3-fold difference between the average daily maximal TSH (3 mIU/ml) and minimal TSH (1 mIU/ml).)

Variations in the biological activity of TSH


Figure 2: Increased risks of disease and premature death at serum TSH levels within the reference range
Graphique 2 : Risques augmentés de maladies et mort prématurée à des taux sériques de la TSH à l’intérieur de l’intervalle statistique de référence.

Body mass index: lowest values at serum TSH levels below the 0.4 mIU/mL.

**Thyroid cancer: lowest risks at serum TSH levels below the 0.4 mIU/mL**

50.  [17] Kumar H, Daykin J, Holder R, Watkinson JC, Sheppard MC, Franklyn JA. Gender, clinical findings, and serum thyrotropin measurements in the prediction of thyroid neoplasia in 1005 patients presenting with thyroid enlargement and investigated by fine-needle aspiration cytology. Thyroid. 1999 Nov;9(11):1105-9. Department of Medicine, University of Birmingham, Queen Elizabeth Hospital, Edgbaston, United Kingdom

**Tighter serum TSH reference interval, i.e. 0.4–2.0 mU/liter, when data for subjects with positive TPOAb or a family history of autoimmune thyroid disease are excluded.** This tighter reference range may certainly be more applicable to African-Americans, who have a lower mean TSH


**The mean serum TSH of a population is around the 1.5 mIU/mL**

53.  [19] Wartofsky L, Dickey RA. The evidence for a narrower thyrotropin reference range is compelling. J Clin Endocrinol Metab. 2005 Sep;90(9):5483-8. (“a personal range of 0.5–1.0 mU/liter would be at subphysiological thyroid hormone levels at the population mean TSH of 1.5 mU/liter (as explained by Wartofsky 2005”)’

**Ethnic differences: the mean TSH level in African-Americans is 1.18 mU/liter.**


**The individual serum TSH reference range is (much) narrower for individuals**

55. Andersen S, Petersen KM, Brunn NH, Laurberg P. Narrow individual variations in serum T4 and T3 in normal subjects: a clue to the understanding of subclinical thyroid disease. J Clin Endocrinol Metab. 2002;87:1068–72

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**Figure 3:** Serum testosterone threshold levels beneath which mortality and risks of disease increase

*Graphique 3*: Seuils de taux sanguins de testostérone sous lesquels la mortalité et/ou le risque de maladie augmente

**TESTOSTERONE DEFICIENCIES in MEN with SERUM ANDROGEN LEVELS within the REFERENCE RANGE: to TREAT or NOT to TREAT? Should men with symptoms and signs of testosterone deficiency, but serum androgen levels within the normal reference range for their age, be treated with testosterone?**

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**Critics against the value of laboratory tests and their reference ranges to evaluate androgen deficiency**

**Wide intraindividual fluctuations in blood test results** for serum total, free and bioavailable testosterone (T), dihydrotestosterone (DHT), SHBG, LH, dehydroepiandrosterone (DHEA), dehydroepiandrosterone sulphate (DHEAS), oestrone, oestradiol and cortisol: one sample is generally not sufficient to characterize an individual's hormone levels
1. Brambilla DJ, O'Donnell AB, Matsumoto AM, McKinlay JB. Intraindividual variation in levels of serum testosterone and other reproductive and adrenal hormones in men. Clin Endocrinol (Oxf). 2007 Dec;67(6):853-62. New England Research Institutes, Watertown, Massachusetts, USA. (Paired blood samples were obtained 1-3 days apart at entry and again 3 months and 6 months later (maximum six samples per subject). Each sample consisted of a pool of equal aliquots of two blood draws 20 min apart. Study participants were men aged 30-79 years; the intraindividual standard deviations imply that a clinician can expect to see a difference exceeding 18-28% about half the time when two measurements are made on a subject. The difference will exceed 27-54% about a quarter of the time.)

Wide variability in the reference range for serum testosterone

2. Lazarou S, Reyes-Vallejo L, Morgentaler A. Wide variability in laboratory reference values for serum testosterone. J Sex Med. 2006 Nov;3(6):1085-9. Harvard Medical School, Division of Urology, Beth Israel Deaconess Medical Center, Boston, MA, USA. (Of the 25 labs, there were 17 and 13 different sets of reference values for total and free testosterone, respectively. The low reference value for total testosterone ranged from 130 to 450 ng/dL (350% difference), and the upper value ranged from 486 to 1,593 ng/dL (325% difference). Age-adjusted reference values were applied in four centers for total testosterone and in seven labs for free testosterone. All reference values were based on a standard statistical model without regard for clinical aspects of hypogonadism. Twenty-three of the 25 lab directors responded that clinically relevant testosterone reference ranges would be preferable to current standards. CONCLUSIONS. Laboratory reference values for testosterone vary widely, and are established without clinical considerations.)

The higher young adult reference range for serum testosterone is a better reference range to detect androgen deficiency in men with androgen deficiency symptoms


Table: Divergence between the % of men with androgen deficiency complaints going to a clinic and the % of them below the testosterone reference range

| % of Men with androgen deficiency symptoms (Partial androgen deficiency in the aging male or PADAM-like symptoms) | 100% |
| % of Men with free testosterone levels below the normal range of men in their twenties (15.2-43.5 pg/ml) | 82% |
| % of Men with free testosterone levels below the normal range of their age (9.3-26.5 pg/ml) | 30% |
| % of Men with total testosterone level below 200 ng/dl (= criterion for testosterone replacement recommended by the American Association of Clinical Endocrinologists guidelines) | 9% |


Poor correlations of the testosterone levels (bioavailable testosterone and calculated free testosterone) with clinical symptoms with in men aged over 70 years

4. Lin YC, Hwang TI, Chiang HS, Yang CR, Wu HC, Wu TL, Huang SP. Correlations of androgen deficiency with clinical symptoms in Taiwanese males. Int J Impot Res. 2006 Jul-Aug;18(4):343-7 Division of Urology, Department of Surgery, Shin-Kong WHS Memorial Hospital, Taipei, Taiwan, ROC. (An androgen deficiency questionnaire might not be a suitable single and should be used together with biochemical markers for evaluation of for androgen deficiency)

Studies that show disease and mortality to be associated with testosterone levels within the (laboratory) reference range

The findings of these studies support the view that men who may have testosterone levels within the reference, but complain of having testosterone deficiency symptoms might need and benefit from testosterone treatment
Studies that show that subjects who are at or below the 90th percentile of serum testosterone levels have an increased risk of disease or dying: this concerns most studies that show an inverse association between testosterone levels and the risk of disease/dying

Increased overall, cardiovascular and cancer mortality in men aged 40 to 79 years

5. Khaw KT, Dowsett M, Folkerd E, Bingham S, Wareham N, Luben R, Welch A, Day N. Endogenous testosterone and mortality due to all causes, cardiovascular disease, and cancer in men: European prospective investigation into cancer in Norfolk (EPIC-Norfolk) Prospective Population Study. Circulation. 2007 Dec 4;116(23):2694-701 Clinical Gerontology Unit Box 251, Addenbrooke’s Hospital, Cambridge CB2 2QK, UK. kk101@medschl.cam.ac.uk (An increase of 6 nmol/L (173 ng/dl or 1730 pg/ml) serum testosterone (approximately 1 SD) was associated in men aged 40 to 79 years followed up for 6 to 10 years with a significant 19% reduction in overall mortality; Inverse relationships were also observed for deaths due to cardiovascular and cancer)

Impaired cognitive function in men between 61 and 72 years

6. Hogervorst E, De Jager C, Budge M, Smith AD. Serum levels of estradiol and testosterone and performance in different cognitive domains in healthy elderly men and women. Psychoneuroendocrinology. 2004 Apr;29(3):405-21. Oxford Project to Investigate Memory and Ageing and the Department of Pharmacology, University of Oxford and Radcliffe Infirmary Trust, Oxford, OX2 6HE, UK. eva.hogervorst@pharm.ox.ac.uk (Men between 61 and 72 years of age had a positive relationship between high total testosterone levels and speed of information processing)

Higher plasma amyloid beta peptide 40, a risk factor for Alzheimer’s disease, in older men with subjective memory loss or dementia

7. Gillett MJ, Martins RN, Clarinette RM, Chubb SA, Bruce DG, Yeo BB. Relationship between testosterone, sex hormone binding globulin and plasma amyloid beta peptide 40 in older men with subjective memory loss or dementia. J Alzheimers Dis. 2003 Aug;5(4):267-9. Department of Endocrinology and Diabetes, Fremantle Hospital, Western Australia, Australia. (In older men with either subjective memory loss or dementia, serum total and calculated free testosterone correlated significantly and inversely with plasma levels of amyloid beta peptide 40)

Alzheimer’s disease in older men


Dyslipidemia

Higher serum triglycerides and lipoprotein a


10. Zhao SP, Li XP. The association of low plasma testosterone level with coronary artery disease in Chinese men. Int J Cardiol. 1998 Jan 31;63(2):161-4. Department of Cardiology, Second Affiliated Hospital, Hunan Medical University, Changsha, P.R. China. (Negative association between plasma total testosterone level and plasma triglyceride level (P<0.001) and lipoprotein a)

Lower serum HDL cholesterol and higher serum apo B100 and lipoprotein a in healthy men and men with coronary heart disease


A significant positive correlation was found between testosterone and HDL-cholesterol.

**Higher serum triglycerides and total and LDL cholesterol in men primary prostate carcinoma after castration**

13. Xu T, Wang X, Hou S. Effect of lower androgen levels on arteriosclerosis. Zhonghua Wai Ke Za Zhi. 2001 Sep;39(9):698-701. Department of Urologic Surgery, People's Hospital, Peking University, Beijing 100044, China. (Negative linear correlations were found between total testosterone and free testosterone serum levels and triglyceride, total cholesterol, LDL cholesterol in men primary prostate carcinoma after castration)

**Higher serum glucose and insulin in men at 67 years of age**


**In men primary prostate carcinoma after castration**

15. Xu T, Wang X, Hou S. Effect of lower androgen levels on arteriosclerosis. Zhonghua Wai Ke Za Zhi. 2001 Sep;39(9):698-701. Department of Urologic Surgery, People's Hospital, Peking University, Beijing 100044, China. (Negative linear correlation between total testosterone and free testosterone serum levels and fasting insulin and glucose, 2 h insulin and glucose in men primary prostate carcinoma after castration)

**Excessive coagulation in men primary prostate carcinoma after castration**

16. Xu T, Wang X, Hou S. Effect of lower androgen levels on arteriosclerosis. Zhonghua Wai Ke Za Zhi. 2001 Sep;39(9):698-701. Department of Urologic Surgery, People's Hospital, Peking University, Beijing 100044, China. (Negative linear correlation between total testosterone and free testosterone serum levels and plasma fibrinopeptide A, plasminogen activator inhibitor-1 in men primary prostate carcinoma after castration)

**Increased atherosclerosis (carotid artery intima-media thickness)**

**In men aged 25-84 years**

17. Svartberg J, von Mühlen D, Mathiesen E, Joakimsen O, Bønaa KH, Stensland-Bugge E. Low testosterone levels are associated with carotid atherosclerosis in men. J Intern Med. 2006 Jun;259(6):576-82. Department of Medicine, University Hospital of North Norway, Tromsø, Norway. johan.svartberg@unn.no (... found an inverse association between total testosterone levels and intima media thickness of the carotid artery in men aged 25-84 years)

**In middle-aged men**

18. Mäkinen J, Järvisalo MJ, Pöllänen P, Perheentupa A, Irlaja K, Koskenvuo M, Mäkinen J, Huhtaniemi I, Raitakari OT. Increased carotid atherosclerosis in andropausal middle-aged men. J Am Coll Cardiol. 2005 May 17;45(10):1603-8. Research Centre of Applied and Preventive Cardiovascular Medicine, University of Turku, Turku, Finland. (Common carotid artery intima-media thickness correlated inversely with serum testosterone (p = 0.003) and directly with LH (p = 0.006) in middle-aged men, 40- to 70-year-old men (mean age 57 years))

**In elderly men**

19. Muller M, van den Beld AW, Bots ML, Grobbee DE, Lamberts SW, van der Schouw YT. Endogenous sex hormones and progression of carotid atherosclerosis in elderly men. Circulation. 2004 May 4;109(17):2074-9. Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, The Netherlands. (Serum free testosterone was inversely related to the mean progression of carotid intima-media thickness in elderly men)

20. van den Beld AW, Bots ML, Janssen JA, Pols HA, Lamberts SW, Grobbee DE. Endogenous hormones and carotid atherosclerosis in elderly men. Am J Epidemiol. 2003 Jan 1;157(1):25-31. Department of Internal Medicine, Erasmus University Medical Center Rotterdam, Rotterdam, The Netherlands. vanderbeld@inw3.azr.nl (Serum testosterone, estrone, and free IGF-I were inversely related to intima-media thickness. The strength of these relations was as powerful in subjects with as in those without prevalent cardiovascular disease)

**Arterial stiffness**

**Increased pulse wave velocity in men with type 2 diabetes mellitus**

22. Fukui M, Ose H, Kitagawa Y, Yamazaki M, Hasegawa G, Yoshikawa T, Nakamura N. Relationship between low serum endogenous androgen concentrations and arterial stiffness in men with type 2 diabetes mellitus. Metabolism. 2007 Sep;56(9):1167-73 Department of Endocrinology and Metabolism, Kyoto Prefectural University of Medicine, Graduate School of Medical Science, Kawaramachi-Hirokoji, Kyoto, Japan. sayarinapm@hotmail.com *(Pulse wave velocity (PWV) was significantly +7.5% greater in patients with lower concentrations of free testosterone (<10 pg/mL) than in patients with higher concentrations of free testosterone. Inverse correlations were found between serum free testosterone concentration and PWV (P = .0003) in men with type 2 diabetes mellitus.)*

**Peripheral arterial disease in elderly men**

23. Tivesten A, Meliström D, Jutberger H, Fagerberg B, Lernfelt B, Orwell E, Karlsson MK, Ljunggren O, Ohlsson C. Low serum testosterone and high serum estradiol associate with lower extremity peripheral arterial disease in elderly men. The MrOS Study in Sweden. J Am Coll Cardiol. 2007 Sep 11;50(11):1070-6 The Wallenberg Laboratory for Cardiovascular Research, Göteborg University, Göteborg, Sweden. asa.tivesten@medic.gu.se *(Low serum testosterone and high serum estradiol levels associate with lower extremity peripheral arterial disease (defined as ankle-brachial index <0.90) in elderly men mean age 75.4 years); Free testosterone independently and positively associates with ankle-brachial index (p < 0.001).)*

**Higher diastolic blood pressure and low ejection fraction in men with coronary heart disease**

24. Dobrzycki S, Serwatka W, Nadlewski S, Kurecki J, Jackowski R, Paruk J, Ladny JR, Hirnle T. An assessment of correlations between endogenous sex hormone levels and the extensiveness of coronary heart disease and the ejection fraction of the left ventricle in males. J Med Invest. 2003 Aug;50(3-4):162-9. Department of Invasive Cardiology, Białystok University Medical Center, 24 A. M. Sklodowskiej-Curie St., 15-276 Białystok, Poland. *(Lower levels of total testosterone in men with proven coronary heart disease were associated to higher diastolic blood pressure and higher DUKE index (low ejection fraction).*

**Higher systolic blood pressure in healthy men and men with coronary heart disease**


**Increased severity of heart failure in chronic heart failure patients**


**Loss of muscle mass (sarcopenia) and strength and fitness**


**Loss of muscle strength and work capacity in middle-aged and elderly men**

Loss of muscle mass and exercise capacity


Loss of muscle mass and exercise capacity

29. Grinspoon S, Corcoran C, Lee K, Burrows B, Hubbard J, Katznelson L, Walsh M, Guccione A, Cannan J, Heller H, Basgoz N, Klibanski A. Loss of lean body and muscle mass correlates with androgen levels in hypogonadal men with acquired immunodeficiency syndrome and wasting. J Clin Endocrinol Metab. 1996 Nov;81(11):4051-8. (Free-testosterone levels were correlated with total body potassium (R = 0.45, P < 0.05) and muscle mass (R = 0.45, P < 0.05). Total-testosterone levels were correlated with exercise functional capacity)

Low bone mineral density in healthy men aged 43-73 years


Metabolic Syndrome

In aging men

32. Muller M, Grobbee DE, den Tonkelaar I, Lamberts SW, van der Schouw YT. Endogenous sex hormones and metabolic syndrome in aging men. J Clin Endocrinol Metab. 2005 Aug;90(8):4979; author reply 4979. J Clin Endocrinol Metab. 2005 Nov;90(11):6339; author reply 6339. Clin Endocrinol Metab. 2005 May;90(5):2618-23. Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, PO Box 85000, Room D 01.335, 3508 GA Utrecht, The Netherlands (Metabolic syndrome was inversely related to serum levels of total testosterone (1 standard deviation increase of circulating total testosterone, reduced the risk of metabolic syndrome by -57%)

In nonsmoking men

33. Blouin K, Despré JP, Coulard C, Tremblay A, Prud'homme D, Bouchard C, Tchernof A. Contribution of age and declining androgen levels to features of the metabolic syndrome in men. Metabolism. 2005 Aug;54(8):1034-40. Molecular Endocrinology and Oncology Research Center, Laval University Medical Research Center, Quebec, Canada G1V 4G2. (The % frequency of men characterized by 3 or more features of the metabolic syndrome increased with decreasing testosterone)

Increased visceral obesity and presence of components of the metabolic syndrome in older men

34. Chen RY, Wittet GA, Andrews GR. Relative androgen deficiency in relation to obesity and metabolic status in older men. Diabetes Obes Metab. 2006 Jul;8(4):429-35. Department of Medicine, University of Adelaide, Adelaide, South Australia, Australia. (Serum total testosterone was inversely related to visceral obesity and several components of the metabolic syndrome)

Higher body fat, visceral fat, body mass index

35. Shimizu W, Matsuo K, Kokubo Y, Satomi K, Kurita T, Noda T, Nagaya N, Suyama K, Aihara N, Kamakura S, Inamoto N, Akahoshi M, Tomoke H. Sex hormone and gender difference—role of testosterone on male predominance in Brugada syndrome. J Cardiovasc Electrophysiol. 2007 Apr;18(4):415-21. Division of Cardiology, Department of Internal Medicine, National Cardiovascular Center, Suita, Osaka, Japan. (Testosterone level was inversely correlated with BMI and body fat % in both groups. Higher testosterone level was associated with lower visceral fat)

of Endocrinology, Diabetes, and Metabolism, State University of New York at Buffalo and Kaleida Health, Buffalo, New York 14209, USA. (Significant inverse correlation of BMI with free testosterone ($r = -0.382$; $P < 0.01$) and total testosterone ($P < 0.01$))

**Highe risk of diabetes** in men aged 55-89 years

37. Oh JY, Barrett-Connor E, Wedick NM, Wingard DL; Rancho Bernardo Study. Endogenous sex hormones and the development of type 2 diabetes in older men and women: the Rancho Bernardo study. J Diabetes Care. 2002 Jan;25(1):55-60. Division of Epidemiology, Department of Family and Preventive Medicine, University of California, San Diego, California 92093-0607, USA. (Total testosterone was inversely and significantly related to subsequent levels of fasting and postchallenge glucose and insulin in men aged 55-89 years)

**Increased risk of prostate cancer**

38. Pourmand G, Salem S, Mehrsai A, Lotfi M, Amirzargar MA, Mazdak H, Roshan AI, Kheirollahi A, Kalantar E, Baradaran N, Saboury B, Allameh F, Karami A, Ahmadi H, Jahani Y. The risk factors of prostate cancer: a multicentric case-control study in Iran. Asian Pac J Cancer Prev. 2007 Jul-Sep;8(3):422-8. Urology Research Center, Medical Sciences/University of Tehran, Sina Hospital, Hassan-Abad Sq., Tehran 1136746911, Iran. salem@farabi.tums.ac.ir. (Increasingly lower levels of testosterone, the testosterone to PSA ratio, dihydrotestosterone with the reference range are associated with prostate cancer: one unit elevation in serum testosterone concentration was related to a -21% significant decrease of prostate cancer risk)

39. Severi G, Morris HA, MacInnis RJ, English DR, Tilley W, Hopper JL, Boyle P, Giles GG. Circulating steroid hormones and the risk of prostate cancer. Cancer Epidemiol Biomarkers Prev. 2006 Jan;15(1):86-91. Cancer Epidemiology Centre, The Cancer Council Victoria, University of Melbourne, Melbourne, Australia. Gianluca.severi@cancervic.org.au. (The risk of prostate cancer was approximately almost halved for a doubling of the concentration of testosterone (HR, 0.55; 95% CI, 0.32-0.95))

40. Karamanolakis D, Lambou T, Bogdanos J, Milathianakis C, Sourla A, Lembassis P, Halapas A, Psissimissis 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. Department of Experimental Physiology, Medical School, University of Athens, Goudi-Athens, Greece. (Testosterone and the testosterone to PSA ratio were inversely and significantly related to prostate cancer. The risk of prostate cancer increasing sharply (12.5 times) with a decrease of the Testosterone to PSA ratio by one standard deviation)

Dihydrotestosterone is strongly and inversely associated with the risk of prostate cancer


**Higher HIV RNA in HIV-positive men**

42. Ferrando SJ, Rabkin JG, Poretsky L. Dehydroepiandrosterone sulfate (DHEAS) and testosterone: relation to HIV illness stage and progression over one year. J Acquir Immune Defic Syndr. 1999 Oct 1;22(2):146-54. Department of Psychiatry, Cornell University Medical College, New York, New York, USA. (Serum free testosterone was inversely correlated with HIV RNA)

**Studies that show that men who are at or below the 33rd percentile (in the lower tertile) of serum testosterone levels have an increased risk of the following diseases:**

**Metabolic syndrome**

*In nonsmoking men*

43. Blouin K, Després JP, Couillard C, Tremblay A, Prud'homme D, Bouchard C, Tchernof A. Contribution of age and declining androgen levels to features of the metabolic syndrome in men. Metabolism. 2005 Aug;54(8):1034-40. Molecular Endocrinology and Oncology Research Center, Laval University Medical Research Center, Quebec, Canada G1V 4G2. (Men in the upper tertile of testosterone levels had a significant -76% lower risk of being characterized by 3 or more features of the metabolic syndrome independent of age)
In middle-aged men

44. Tong PC, Ho CS, Yeung VT, Ng MC, So WY, Ozaki R, Ko GT, Ma RC, Poon E, Chan NN, Lam CW, Chan JC. Association of testosterone, insulin-like growth factor-I, and C-reactive protein with metabolic syndrome in Chinese middle-aged men with a family history of type 2 diabetes. J Clin Endocrinol Metab. 2005 Dec;90(12):6418-23 Department of Medicine and Therapeutics, School of Public Health, The Chinese University of Hong Kong, The Prince of Wales Hospital, Shatin, Hong Kong. ptong@cuhk.edu.hk (The frequency of metabolic syndrome increased with declining tertiles of total testosterone and IGF-1 in men with or without a family history of diabetes (mean age: 39.1 and 43.9 years), but increasing tertiles of serum CRP. After adjustment for age and smoking history, subjects with all three risk factors had a 13-fold increase in risk association with MES compared with those without hormonal and inflammatory risk factors)

Diabetes in men

45. Selvin E, Feinleib M, Zhang L, Rohmann S, Rifai N, Nelson WG, Dobs A, Basaria S, Golden SH, Platz EA. Androgens and diabetes in men: results from the Third National Health and Nutrition Examination Survey (NHANES III). Diabetes Care. 2007 Feb;30(2):234-8. Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, 615 N. Wolfe Street, Baltimore, MD 21205, USA. (Low free and bioavailable testosterone concentrations in the normal range were associated with diabetes, independent of adiposity; Men in the first tertile of bioavailable testosterone were approximately four times as likely to have prevalent diabetes compared with men in the third tertile )

Lower bone mineral density in older men

46. Kenny AM, Prestwood KM, Marcello KM, Raisz LG. Determinants of bone density in healthy older men with low testosterone levels. J Gerontol A Biol Sci Med Sci. 2000 Sep;55(9):M492-7. Center on Aging, University of Connecticut Health Center, Farmington 06030-5215, USA. kenny@NSO1.uchc.edu (Femoral neck bone mineral density mean values were 0.86 g/cm2 for the lowest tertile, 0.94 for the middle tertile, and 0.99 for the highest tertile. 52% of older men with low bioavailable testosterone levels had BMD levels below the young adult normal range associations persisted even after excluding men with clinically abnormal testosterone concentrations defined as total testosterone <3.25 ng/ml or free testosterone <0.07 ng/ml)

Studies that show that subjects who are at or below the 75th percentile (in the lower three quartiles) of serum testosterone levels have an increased risk of dying

Increased overall, cardiovascular and cancer mortality in men aged 40 to 79 years

47. Khaw KT, Dowsett M, Folkerd E, Bingham S, Wareham N, Luben R, Welch A, Day N. Endogenous testosterone and mortality due to all causes, cardiovascular disease, and cancer in men: European prospective investigation into cancer in Norfolk (EPIC-Norfolk) Prospective Population Study. Circulation. 2007 Dec 4;116(23):2694-701 Clinical Gerontology Unit Box 251, Addenbrooke’s Hospital, Cambridge CB2 2QQ, UK. kk101@medschl.cam.ac.uk (For increasing quartiles of endogenous testosterone compared with the lowest quartile: -25 % mortality reduction for the middle low quartile, -38% for the middle high quartile and -41% for the upper quartile)

Studies that show that subjects who are at or below the 25th percentile (in the lower quartile) of serum testosterone levels have an increased risk of disease or dying

Increased overall, cardiovascular and respiratory disease mortality in men aged 50-91 years

48. Laughlin GA, Barrett-Connor E, Bergstrom J. Low serum testosterone and mortality in older men. J Clin Endocrinol Metab. 2008 Jan;93(1):68-75. Department of Family and Preventive Medicine, School of Medicine, University of California, San Diego, 9500 Gilman Drive, MC 0631C, La Jolla, California 92093. glaughlin@ucsd.edu. (Men aged 50-91 (median 73.6) years followed up for 17 to 20 years whose total testosterone levels were in the lowest quartile (<241 ng/dl) were 40% [hazards ratio (HR) 1.40; 95% confidence interval (CI) 1.14-1.71] more likely to die than those with higher levels. Low testosterone predicted increased risk of cardiovascular (HR 1.38; 95% CI 1.02-1.85) and respiratory disease (HR 2.29; 95% CI 1.25-4.20) mortality, but was not significantly related to cancer death (HR 1.34; 95% CI 0.89-2.00).
Increased risk of peripheral arterial disease

49. Tivesten A, Mellström D, Julberger H, Fagerberg B, Lernfelt B, Orwell E, Karlsson MK, Ljunggren O, Ohlsson C. Low serum testosterone and high serum estradiol associate with lower extremity peripheral arterial disease in elderly men. The MrOS Study in Sweden. J Am Coll Cardiol. 2007 Sep 11;50(11):1070-6. The Wallenberg Laboratory for Cardiovascular Research, Göteborg University, Göteborg, Sweden. asa.tivesten@medic.gu.se (Low serum testosterone and high serum estradiol levels are associated with lower extremity peripheral arterial disease (defined as ankle-brachial index <0.90) in elderly men mean age 75.4 years; free testosterone independently and positively associates with ankle-brachial index (p < 0.001)) free testosterone in the lowest quartile (vs. quartiles 2 to 4; odds ratio = 1.65; p = 0.001) and free estradiol in the highest quartile (vs. quartiles 1 to 3; OR 1.45, p = 0.012) independently associate with lower extremity PAD)

Increased risk of diabetes in men aged 55-89 years

50. Oh JY, Barrett-Connor E, Wedick NM, Wingard DL; Rancho Bernardo Study. Endogenous sex hormones and the development of type 2 diabetes in older men and women: the Rancho Bernardo study. Diabetes Care. 2002 Jan;25(1):55-60. Division of Epidemiology, Department of Family and Preventive Medicine, University of California, San Diego, California 92093-0607, USA. (The odds for new diabetes were 2.7 (95% CI 1.1-6.6) for men in the lowest quartile of total testosterone in men in men aged 55-89 years)

Hip bone density loss in older men with weight loss

51. Ensrud KE, Lewis CE, Lambert LC, Taylor BC, Fink HA, Barrett-Connor E, Cauley JA, Stefanick ML, Orwell E; Osteoporotic Fractures in Men MrOS Study Research Group. Endogenous sex steroids, weight change and rates of hip bone loss in older men: the MrOS study. Osteoporos Int. 2006;17(9):1329-36. Department of Medicine 111-0, VA Medical Center, One Veterans Drive, Minneapolis, MN 55417, USA. ensru001@umn.edu (Among older men with weight loss, the rate of decline in total hip bone mineral density showed a stepwise increase in magnitude with greater decreases in bioavailable testosterone from baseline (p value for trend <0.001)

Studies that show that subjects who are at or below the 20th percentile (in the lower quintile) of serum testosterone levels have an increased risk of the following disease:

Increased atherosclerosis (intima media thickness) in men aged 25-84 years

52. Svartberg J, von Mühlen D, Mathiesen E, Joakimsen O, Bønaa KH, Stensland-Bugge E. Low testosterone levels are associated with carotid atherosclerosis in men. J Intern Med. 2006 Jun;259(6):576-82. Department of Medicine, University Hospital of North Norway, Tromsø, Norway. johan.svartberg@unn.no (Men with testosterone levels in the lowest quintile (<9.0 nmol L(-1)) had an independent OR = 1.51 (P = 0.015) of being in the highest intima media thickness quintile)

Studies that show that subjects who are at or below the 10th percentile of serum testosterone levels have an increased risk of dying

Increased mortality in chronic heart failure patients


CUTOFF levels for serum testosterone, below which the risk of disease or death is increased

A number of studies show that men with serum IGF-1 levels within the normal (reference range), but at or below a precise cutoff serum level may at a higher risk of developing a disease or of dying.

The first two tables below presents the reference ranges (95th centile) of plasma total testosterone, SHBG, calculated free testosterone and bioavailable testosterone levels.
<table>
<thead>
<tr>
<th>Patient age group</th>
<th>Total Testosterone nmol/l</th>
<th>SHBG nmol/l</th>
<th>(Sodegard) nmol/l</th>
<th>(Vermeulen) nmol/l</th>
<th>(Nanje-Wheeler) nmol/l</th>
<th>Free Androgen Index</th>
<th>Bioavailable testosterone nmol/l</th>
</tr>
</thead>
<tbody>
<tr>
<td>20–39 years</td>
<td>12.4–26.4</td>
<td>11.7–53.4</td>
<td>0.236–0.680</td>
<td>0.190–0.665</td>
<td>0.256–0.716</td>
<td>29.0–140.6</td>
<td>20-29 yr 2.88–8.92</td>
</tr>
<tr>
<td>40–89 years</td>
<td>4.9–24.4</td>
<td>18.0–67.0</td>
<td>0.117–0.558</td>
<td>0.092–0.552</td>
<td>0.131–0.580</td>
<td>14.4–89.7</td>
<td>40-49 yr 2.12–7.39</td>
</tr>
</tbody>
</table>

Notes: The bioavailable testosterone reference range is obtained from Mayo Clinic at http://www.mayomedicallaboratories.com/test-catalog/Clinical-and-Interpretive/83686; All the other reference ranges from Teoh YP, Wallace AM. Population reference ranges for plasma testosterone and calculated free testosterone in older men. Endocrine Abstracts 200; 12: 104

<table>
<thead>
<tr>
<th>Patient age group</th>
<th>Total Testosterone ng/dl</th>
<th>SHBG mg/l</th>
<th>(Sodegard) pg/ml</th>
<th>(Vermeulen) pg/ml</th>
<th>(Nanje-Wheeler) pg/ml</th>
<th>Free Androgen Index</th>
<th>Bioavailable testosterone ng/dl</th>
</tr>
</thead>
<tbody>
<tr>
<td>40–89 years</td>
<td>141–703</td>
<td>1.71–6.37</td>
<td>34–161</td>
<td>27–159</td>
<td>38–167</td>
<td>14.4–89.7</td>
<td>40-49 yr 61–213</td>
</tr>
</tbody>
</table>

≥70 years Not established
The second table presents the **threshold or cutoff levels** of serum testosterone, below which the risk of disease or death has been reported to significantly increase.

<table>
<thead>
<tr>
<th>The cutoff level is</th>
<th>CUTOFF level of serum Total Testosterone</th>
<th>Morbidity risk BELOW the cutoff level</th>
<th>Reference study</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Within the reference range for serum Testosterone of 40-89 year-old men</td>
<td>250 ng/dl</td>
<td>8.7 nmol/l</td>
<td>Prostate cancer</td>
<td>54. Morgentaler A, Rhoden EL. Prevalence of prostate cancer among hypogonadal men with prostate-specific antigen levels of 4.0 ng/mL or less. Urology. 2006 Dec;68(6):1263-7</td>
</tr>
<tr>
<td></td>
<td>288 ng/dl</td>
<td>10 nmol/l</td>
<td>Depression</td>
<td>57. Zitzmann M, Faber S, Nieschlag E. Association of specific symptoms and metabolic risks with serum testosterone in older men. J Clin Endocrinol Metab. 2006 Nov;91(11):4335-43 Institute of Reproductive Medicine of the University, Domagkstr. 11, D-48129 Münster,</td>
</tr>
<tr>
<td></td>
<td>300 ng/dl</td>
<td>10.4 nmol/l</td>
<td>Type 2 Diabetes</td>
<td>58. Klein RS, Lo Y, Santoro N, Dobs AS. Androgen levels in older men who have or who are at risk of acquiring HIV infection. Clin Infect Dis. 2005 Dec 15;41(12):1794-803</td>
</tr>
<tr>
<td>Within the reference range for serum Testosterone of 20-89 year-old men</td>
<td>449 ng/dl</td>
<td>15.6 nmol/l</td>
<td>Type 2 Diabetes</td>
<td>60. Zitzmann M, Faber S, Nieschlag E. Association of specific symptoms and metabolic risks with serum testosterone in older men. J Clin Endocrinol Metab. 2006 Nov;91(11):4335-43</td>
</tr>
<tr>
<td></td>
<td>449 ng/dl</td>
<td>15.6 nmol/l</td>
<td>Loss of vigor</td>
<td>61. Ding EL, Song Y, Malik VS, Liu S. Sex differences of endogenous sex hormones and risk of type 2 diabetes: a systematic review and meta-analysis. JAMA. 2006 Mar 15;295(11):1288-99</td>
</tr>
<tr>
<td></td>
<td>449 ng/dl</td>
<td>15.6 nmol/l</td>
<td>Loss of libido</td>
<td></td>
</tr>
</tbody>
</table>
## Thresholds or cutoff levels of serum Free Testosterone in men

<table>
<thead>
<tr>
<th>CUTOFF level of serum Free Testosterone</th>
<th>Morbidity risk BELOW the cutoff level</th>
<th>Reference study</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 pg/ml</td>
<td>Increased arterial stiffness</td>
<td>63. Fukui M, Ose H, Kitagawa Y, Yamazaki M, Hasegawa G, Yoshikawa T, Nakamura N. Relationship between low serum endogenous androgen concentrations and arterial stiffness in men with type 2 diabetes mellitus. Metabolism. 2007 Sep;56(9):1167-73</td>
<td>In men with type 2 diabetes mellitus</td>
</tr>
<tr>
<td>17.3 pg/ml</td>
<td>Premature coronary disease</td>
<td>64. Turhan S, Tulunay C, Gülçü S, Ozdöl C, Kilickap M, Altin T, Gerede M, Erol C. The association between androgen levels and premature coronary artery disease in men. Coron Artery Dis. 2007 May;18(3):159-62</td>
<td>Below the cut-off value of 17.3 pg/ml had an adjusted 3.3-fold risk of developing premature coronary artery disease</td>
</tr>
</tbody>
</table>

### Thresholds or cutoff levels of serum bioavailable testosterone for disease within the reference range

<table>
<thead>
<tr>
<th>CUTOFF level of serum Bioavailable Testosterone</th>
<th>Morbidity risk BELOW the cutoff level</th>
<th>Reference study</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>100 ng/dl</td>
<td>Severe erectile dysfunction</td>
<td>66. Kratzik CW, Schatzl G, Lungimayr G, Rücklinger E, Huber J. The impact of age, body mass index and testosterone on erectile dysfunction. J Urol. 2005 Jul;174(1):240-3</td>
<td>Low bioavailable testosterone (&lt; 1 ng/ml) =&gt; 3 x higher risk of severe erectile dysfunction</td>
</tr>
</tbody>
</table>

### Studies of diseases that are associated with lower testosterone levels within the reference range of older men, suggesting that the lower levels might contribute to the disease

### Lower health

67. Mohr BA, Guay AT, O'Donnell AB, McKinlay JB. Normal, bound and nonbound testosterone levels in normally ageing men: results from the Massachusetts Male Ageing Study. Clin Endocrinol (Oxf). 2005 Jan;62(1):64-73. New England Research Institutes, Watertown, Massachusetts 02472, USA. BethM@neri.org (Apparently healthy men had significantly higher hormone concentrations at most time points than did not apparently healthy men)
Schizophrenia

68. Räsänen P, Hakko H, Visuri S, Paanila J, Kapanen P, Suomela T, Tiihonen J. Serum testosterone levels, mental disorders and criminal behaviour. Acta Psychiatr Scand. 1999 May;99(5):348-52. Department of Psychiatry, University of Oulu, Finland. (Among schizophrenic males, total (P=0.01) and free testosterone (P=0.01) declined significantly more with age compared to healthy controls and patients with personality disorders, and also correlated with duration of neuroleptic drug use (r=-0.60, P=0.000 for total and r=-0.46, P=0.0001 for free testosterone)

Erectile dysfunction


Infertility

70. Andersson AM, Jørgensen N, Frydelund-Larsen L, Raipert-De Meys E, Skakkebaek NE. Impaired Leydig cell function in infertile men: a study of 357 idiopathic infertile men and 318 proven fertile controls. J Clin Endocrinol Metab. 2004 Jul;89(7):3161-7. Department of Growth and Reproduction, Copenhagen University Hospital, Section GR 5064, Blegdamsvej 9, DK-2100 Copenhagen OE, Denmark. anna@rh.dk (Impaired Leydig cell function in infertile men was associated with lower testosterone and testosterone/LH and higher estradiol, estradiol/testosterone, and LH)

Coronary heart disease

71. Zhao SP, Li XP. The association of low plasma testosterone level with coronary artery disease in Chinese men. Int J Cardiol. 1998 Jan 31;63(2):161-4. Department of Cardiology, Second Affiliated Hospital, Hunan Medical University, Changsha, P.R. China. (Low plasma TTT level may be a risk factor for CHD) mean plasma total testosterone levels inpatients with coronary heart (252+/-125 ng/ml) was significantly -39% lower than in the healthy subjects (412+/-309 ng/ml)

72. Chearskul S, Charoenlarp K, Thongtang V, Nitiyanant W. Study of plasma hormones and lipids in healthy elderly Thais compared to patients with chronic diseases: diabetes mellitus, essential hypertension and coronary heart disease. J Med Assoc Thai. 2000 Mar;83(3):266-77. Department of Physiology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand. (Men with coronary heart disease had the lowest testosterone levels compared with men with essential hypertension or non-insulin dependent diabetes mellitus)

Higher fat mass

73. Vandenput L, Mellström D, Lorentzon M, Swanson C, Karlsson MK, Brandberg J, Lönn L, Orwoll E, Smith U, Labrie F, Ljunggren O, Tivesten A, Ohlsson C. Androgens and glucuronidated androgen metabolites are associated with metabolic risk factors in men. J Clin Endocrinol Metab. 2007 Nov;92(11):4130-7 Department of Internal Medicine, Gothenburg University, SE-41345 Gothenburg, Sweden. (BENEFICIAL Both dihydrotestosterone and testosterone were negatively associated with different measures of fat mass in both cohorts; ADVERSE:: androstenediol glucuronide was independently positively associated with fat mass (P < 0.001))

Higher body mass index and waist to hip ratio

74. Rhoden EL, Ribeiro EP, Teloken C, Souto CA. Diabetes mellitus is associated with subnormal serum levels of free testosterone in men. BJU Int. 2005 Oct;96(6):667-70. Urology, Federal Foundation of Medical Sciences of Porto Alegre, Porto Alegre, RS, Brazil. emanrhdon@yahoo.com.br (Subnormal total testosterone levels were more strongly associated with elevated BMI and WHR (OR 2.6; 95%CI 1.7-3.9 and 2.0; 1.4-2.9))

Obesity

75. Allan CA, Strauss BJ, Burger HG, Forbes EA, McLachlan RI. The association between obesity and the diagnosis of androgen deficiency in symptomatic ageing men. Med J Aust. 2006 Oct 16;185(8):424-7. Prince Henry's Institute, Melbourne, VIC, Australia. (Men aged 54-86 years with mean BMI 27.3. Obese men (BMI > or = 30.0 kg/m2 or WC > or = 102 cm) had a significant -15% lower total testosterone (TT) (12.7 nmol/L (366 ng/dl) v15.0 4 nmol/L (432 ng/dl); P < 0.001) and -8% lower calculated free testosterone (275.7 v 299.3 +/- 7.4 pmol/L); P = 0.03 levels than non-obese men)
Diabetes

76. Chen RY, Wittert GA, Andrews GR. Relative androgen deficiency in relation to obesity and metabolic status in older men. Diabetes Obes Metab. 2006 Jul;8(4):429-35. Department of Medicine, University of Adelaide, Adelaide, South Australia, Australia. cheny10@hotmail.com (Total testosterone levels were significantly -15 % lower in diabetic men (mean age of 76.2 years) compared with non-diabetic men (12.1 +/- 0.7 vs. 14.2 visceral obesity and several components of the metabolic syndrome in men with a mean age of 76.2 +/- 0.3 years who were followed up for 8 years)

77. Rhoden EL, Ribeiro EP, Teloken C, Souto CA. Diabetes mellitus is associated with subnormal serum levels of free testosterone in men. BJU Int. 2005 Oct;96(6):867-70. Urology, Federal Foundation of Medical Sciences of Porto Alegre, Porto Alegre, RS, Brazil. emanhiroden@yahoo.com.br (Free and total testosterone serum levels were subnormal in 46% and 34% of diabetics, respectively, and in 24% and 23% of nondiabetics. Subnormal FT levels were strongly correlated with DM (odds ratio (OR) 2.7; 95% confidence interval (CI) 1.8-4.1) but not with elevated BMI (OR 1.4; 95% CI 1.0-2.0)

78. Ding EL, Song Y, Malik VS, Liu S. Sex differences of endogenous sex hormones and risk of type 2 diabetes: a systematic review and meta-analysis. JAMA. 2006 Mar 15;295(11):1288-99. Division of Preventive Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Mass, USA (The testosterone level was -76.6 ng/dl significantly lower on the average in men with type 2 diabetes)

Rheumatoid disease

79. Jiménez-Balderas FJ, Tápia-Serrano R, Fonseca ME, Arellano J, Beltrán A, Yáñez P, Camargo-Coronel A, Fraga A. High frequency of association of rheumatic/autoimmune diseases and untreated male hypogonadism with severe testicular dysfunction. Arthritis Res. 2001;3(6):362-7. Departmento de Reumatología, Hospital de Especialidades, Centro Médico Nacional SXXI IMSS México, DF, México. fjjimenez19@yahoo.com (Surprisingly high frequencies of rheumatic/autoimmune diseases in this small group of patients with untreated hypogonadism (P < 0.001) and very low serum testosterone levels (P = 0.0005)

Lower bone mineral density

80. Van Pottelbergh I, Goemaere S, Zmierczak H, Kaufman JM. Perturbed sex steroid status in men with idiopathic osteoporosis and their sons. J Clin Endocrinol Metab. 2004 Oct;89(10):4949-53. Department of Endocrinology, Unit for Osteoporosis and Metabolic Bone Diseases, Ghent University Hospital, B-9000 Ghent, Belgium. inge.vanpottelbergh@ugent.be (Only in the subgroup of sons belonging to the lowest tertile of lumbar spine BMD was serum free testosteone decreased)

Vertebral fractures

81. Rossini M, Del Marco A, Dal Santo F, Gatti D, Braggion C, James G, Adami S. Prevalence and correlates of vertebral fractures in adults with cystic fibrosis. Bone. 2004 Sep;35(3):771-6. Rheumatology Unit, Osteoporosis Center, University of Verona, 37122, Verona, Italy. maurizio.rossini@libero.it (Significantly lower serum estradiol and free testosterone levels were observed in men with vertebral fractures)

Men with higher serum testosterone levels have more lean mass


New tests and treatments in anti-aging medicine are scientific and validated

Les tests et traitements nouveaux de la médecine anti-âge sont scientifiques et validés

24-hour urinary thyroid hormone tests

60. Tal E, Sulman FG. Urinary thyroxine. Lancet. 1972, 1291

35
66. Ali Afrasiabi M, Dabir Vaziri N, Grant Gwinnup, Mays, Barton CH, Ness RL, Valenta LJ. Thyroid function in the nephrotic syndrome. Ann Int Med. 1979; 90, 335-8
75. Hertoghe J. The usefulness of evaluating the urinary excretion of triiodothyronine and thyroxine in the urines of 24 hours for diagnosis of thyroid dysfunction and follow-up of thyroid treatment. Conference in Antwerp, Belgium, March 1975
77. Hertoghe T. The efficacy of diagnosing borderline and overt hypothyroidism with the laboratory assessment of triiodothyronine and thyroxine excretion in the urines of 24 hours. A comparison with plasma thyroid tests. Optimal hormone therapy in the aging adult. Basic and advanced seminar, San Francisco, February, 2000

**Dissicated thyroid or T4/T3 combinations are better than thyroxine alone as a treatment for hypothyroidism**


**T3-T4 (and T3) treatments work better than T4**

T3-T4 treatment: adding T3 to T4 results in greater improvement of clinical symptoms and signs in hypothyroid patients

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

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

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 classical T4 medication

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

T3 is much more potent than T4

No, well-dosed hormone treatments do not produce more cancer or cardiac disorders, it is often the opposite
Non, les traitements hormonaux bien dosés ne donnent pas plus de cancer ou de troubles cardiaques, c’est souvent même le contraire

Arterial hypertension: the improvement with GH treatment
97. van Dijk M, Bannink EM, van Pareren YK, Mulder PG, Hokken-Koelega AC. Risk factors for diabetes mellitus type 2 and metabolic syndrome are comparable for previously growth hormone-treated young
Cardiovascular mortality: the reduction with GH treatment

Growth hormone therapy increases first the glycemia, then reduces it when given to HIV-infected patients with fat accumulation
100. (26) 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”)

Prostate cancer: testosterone therapy does not increase the risk of prostate cancer, making e.g. a prostate cancer progress from a preclinical to a clinical stage
101. 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.”)
102. Basarà 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”)
103. 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”)
106. 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”)
107. (27) 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”)

TESTOSTERONE TREATMENT AND PROSTATE CANCER

Old view: “Testosterone is a cause or favoring factor of prostate cancer”.

Development of prostate cancer: the generation and progression of prostate cancer depends on androgens.

Treatment of prostate cancer: should consist of androgen deprivation => The use of androgens is contraindicated in prostate cancer patients.

Scientific support: poor originated with one study in 1941 on a single patient by Huggins and coworkers – and some in vitro studies
New view: “Testosterone does not cause, nor favor the development of prostate cancer; adequate testosterone levels are necessary in men for a good quality of life, a good health and for longevity”

Development of prostate cancer: nor the generation nor progression of prostate cancer depends on androgenes. Testosterone and other andrognes are not adversely associated with prostate cancer. On the contrary studies suggest protective effects of higher serum androgens levels on tumor progression (evolution to more malignant forms), next to evident quality of life and global health benefits.

Treatment of prostate cancer: should generally not consist of androgen deprivation. Androgen deprivation has no beneficial effect on survival, but does systematically lower the quality of life and global health => Physicians cannot really justify withholding testosterone replacement from symptomatic hypogonadal patients after they have been successful treated for prostate cancer.

Scientific support: large body of evidence supporting the lack of association of testosterone with prostate cancer or the existence of protective effects of testosterone against prostate cancer progression. Extensive research has confirmed the quality of life and health of testosterone supplementation.

Prostate cancer: Epidemiology

Studies that show there is a high incidence of prostate cancer in the general male population (globally not on testosterone treatment)

1. Fradet Y, Klotz L, Trachtenberg J, Zlotta A. The burden of prostate cancer in Canada. Can Urol Assoc J. 2009 Jun;3(3 Suppl 2):S92-S100. (1 in 7 men will develop (a detected) prostate cancer during their lifetime, and another 1 in 27 will die because of it)
2. Sakr WA, Grignon DJ, Haas GP, Schomer KL, Heilbrun LK, Cassin BJ, Powell J, Montie JA, Pontes JE, Crissman JD. Epidemiology of high grade prostatic intraepithelial neoplasia. Pathol Res Pract. 1995 Sep;191(9):838-41. (85% of Afro-Americans and 63% of Caucasians 70 to 79 years have high grade prostatic intraepithelial neoplasia)

On the very high incidence of prostate cancer when biopsies are made in men aged 62 or over, even with low serum PSA

4. Meikle AW, Stanish WM. Familial prostatic cancer risk and low testosterone. J Clin Endocrinol Metab. 1982 Jun;54(6):1104-8 (Among the 2950 men (age range, 62 to 91 years), prostate cancer was diagnosed in 15.2 %; 14.9 % of the prostate cancers had a Gleason score of 7 or higher. The prevalence of prostate cancer was 6.6 % among men with a PSA level of up to 0.5 ng/ml, 10.1 % among those with values of 0.6 to 1.0 ng/ml, 17.0 % among those with values of 1.1 to 2.0 ng/ml, 23.9 % among those with values of 2.1 to 3.0 ng/ml, and 26.9 % among those with values of 3.1 to 4.0 ng/ml. The prevalence of high-grade cancers increased from 12.5 % of cancers associated with a PSA level of 0.5 ng/ml, or less to 25.0 % of cancers associated with a PSA level of 3.1 to 4.0 ng/ml. Conclusions: biopsy-detected prostate cancer, including high-grade cancers, is not rare among men with PSA levels of 4.0 ng per milliliter or less — levels generally thought to be in the normal range.)

On the real incidence of prostate cancer: much higher prevalence rate of prostate cancer are found at post-mortem (autopsy)


39
Prostate cancer patients have a low risk of dying from cancer

Stemmermann GN, Nomura AM, Chyou PH, Yatani R. A prospective comparison of prostate cancer at autopsy and as a clinical event: the Hawaii Japanese experience. Cancer Epidemiol Biomarkers Prev. 1992 Mar-Apr;1(3):189-93. (“Prostate cancer was diagnosed in life among 274 of 8006 (3.6%) members of a cohort of Japanese men in Hawaii between 1965 and 1990. Only 55 (20%) of these cancers was less than 150 mm³. These small tumors would probably not have been discovered in a screening program. Tumors larger than 1000 mm³ would probably be discovered using modern diagnostic procedures but were found in only 13 (4.4%) of the autopsied men.”)

Quality of life in prostate cancer patients taking androgen deprivation therapy

Dacal K, Sereika SM, Greenspan SL. Quality of life in prostate cancer patients taking androgen deprivation therapy. J Am Geriatr Soc. 2006 Jan;54(1):85-90. (“Participants receiving androgen deprivation therapy (ADT) reported significantly poorer quality of life in the areas of physical function (P<.001), general health (P<.001), and physical health component summary (P<.001) than men not receiving ADT; After controlling for comorbidity, total testosterone level rather than ADT accounted for a small yet statistically significant percentage of the total variance of the physical health...”)

Side effects of testosterone/androgen deprivation therapy of prostate cancer

Androgen deprivation therapy may severely impair the quality of life

several other changes, including hot flashes; gynecomastia; changes in body composition, metabolism, and the cardiovascular system; osteoporosis; anemia; psychiatric and cognitive problems; and fatigue and diminished quality of life”

**Androgen deprivation causes anemia**

**Androgen deprivation causes impotence**

**Androgen deprivation therapy may cause urinary incontinence**

**Androgen deprivation therapy generates a greater rate of bone loss in men with prostate cancer**

**Testosterone deprivation therapy increases arterial stiffness in men with prostate cancer**

**Dihydrotestosterone deprivation therapy increases the risk of aggressive prostate cancer**

**Arguments against population-based PSA screening for prostate cancer and against treatment of prostate cancer**

1. High prevalence rates of prostate cancer at postmortem
2. Increasing biopsy rates lead to overdiagnosis and overtreatment
3. Despite widespread use of such tests in the USA, and apparent incidence rates of detected prostate cancer almost 3 times higher than in the U.K., the mortality in the USA has for many years been almost the same as in the U.K. and other European countries
4. 1/3 of screen-detected cases are incurable
5. No clear benefit of treatment
6. Side effects of prostatectomy include impotence in a large proportion of cases and incontinence in a smaller proportion
7. Screening and follow-up of treatment (much of which may be unnecessary) is expensive (high costs)
8. Few years of life to gain in many elderly patients
9. No consequent reduction in mortality has yet been demonstrated in a randomized controlled trial


**Reasons why the old concept on testosterone treatment and prostate cancer still predominates in the mind of many physicians:**
OLD THEORY: The concept that testosterone feeds a prostate cancer tumor “arose from the work of Huggins and coworkers, who in 1941 demonstrated dramatic responses to castration among men with advanced prostate cancer. These authors and others also reported a rapid clinical progression with testosterone administration.”

CRITICAL OBSERVATIONS: the theory “originated with observations in a special population (castrated men) that is not particularly relevant to testosterone therapy in hypogonadal men” …. Fowler and Whitmore showed in 1981 “that the adverse effect of testosterone treatment did not occur unless men had been previously castrated” …. “More recent studies have failed to provide clinical evidence supporting the belief that higher testosterone represents a risk for prostate cancer”.

FACTORS CONTRIBUTING TO THE PERSISTENCE OF THE ‘testosterone is a cause or favoring factor of prostate cancer’ THEORY include

- dramatic effects of castration
- continued use of androgen deprivation for treatment of prostate cancer
- an influential spokesperson (Huggins)
- group think (failure to acknowledge evidence inconsistent with the prevalent ideology)
- an imprecise formulation of the model (“more T, more cancer growth”), making refutation difficult.


ARGUMENTS PRO 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;

31. 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)
32. 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)
33. 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)
34. 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)
37. 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)

38. 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")

39. 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")

40. 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 levels appears to increase the risk of prostate cancer

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


Low serum testosterone is associated with an increased prostate cancer risk


45. 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


Close to statistical significance lower testosterone levels in prostate cancer patients

60. 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


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


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


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


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


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


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


Studies where close to statistical significance lower DHT levels were found in prostate cancer patients
A low serum level of androstanediol glucuronide, the major androgen metabolite, increases the risk of prostate cancer

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

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

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


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


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

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


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


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

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)


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

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


Men with chronic prostatitis have often low testosterone

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

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

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

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


Studies where testosterone treatment appears to protect against prostate cancer


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


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


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

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


117. Markham MJ. The clinical use of peroral methyltestosterone in benign prostatic hypertrophy. Urol Cutan Rev. 1942; 46; 225

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


120. South Med J, 1939, 32: 154
Study where testosterone treatment reduces prostate stromal hyperplasia and prostatic complaints (prostatism)
121. South Med J, 1939, 32: 154

Studies where dihydrotestosterone treatment reduced the prostate volume (-15 to -20% after 1 year treatment)
124. 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

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

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

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

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

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

A study where testosterone treatment reduces the proliferation of guinea pig prostate stroma cells in vitro
A study where testosterone treatment at high doses does not increase the incidence of prostate cancer cells in mice

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

A study that shows that testosterone treatment of castrated mice can inhibit the progression of androgen-independent prostate cancer in vivo
135. Jennbacken K, Gustavsson H, Tesan T, Horn M, Vaillbo 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

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

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

A study where dihydrotestosterone treatment stimulates apoptosis of prostate cancer cells

Breast Cancer in women: protection with testosterone or dihydrotestosterone treatment?

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
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.")

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")

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")

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")


Prehn RT. On the prevention and therapy of prostate cancer by androgen administration. Cancer Res. 1999 Sep 15;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")

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):1179-85 (the incidence of prostate cancer among men with late-onset hypogonadism on testosterone replacement therapy is no greater than that in the general population)

Dobs AS, Morgenthaler 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")

Morgenthaler 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")

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

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

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


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


Studies with no correlation between serum testosterone and serum PSA


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


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

175. 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


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

STUDIES where testosterone/androgen treatments have no adverse effect on the progression or recurrence of the cancer, but improves quality of life and overall health

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

178. 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”)  

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

180. Agarwal PK, Oefeine 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


183. Kaufman JM, Graydon RJ. Androgen replacement after curative radical prostatectomy for prostate cancer in hypogonadal patients. J Urol. 2005 Feb;173(2):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)  

ANECDO TAL STUDIES that show that testosterone treatment of prostate cancer patients did not accelerate the cancer progression

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


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

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


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


Studies where dihydrotestosterone treatment had no significant effect on serum PSA


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


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


Testosterone treatment does not increase the incidence of prostate disease


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


Studies where DHT treatment had no effect on the prostate volume
ARGUMENTS CONTRA TESTOSTERONE THERAPIES

Studies that suggest that testosterone may increase the prostate cancer risk

Prostate cancer: the association with high free testosterone levels

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

214. 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. (ambiguous study that compares prostate cancer patients with a wrong control group, namely patients with benign prostate hypertrophy (who tend to have an increased conversion of testosterone to estradiol, cause of their stromal hyperplasia) and not to healthy controls with smaller prostates without prostate disease. See Kwon T, et i. BJU Int. 2010 Jan 8. study that shows prostate cancer more easily appears in men with smaller prostate volume, the opposite of benign prostate hypertrophy. In this study, initially higher serum testosterone predict a higher risk of prostate cancer at biopsy, but when prostate cancer is found, higher serum testosterone are associated with less aggressive disease)

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

216. Mydlo JH, Tieng NL, Volpe MA, Chaiken R, Kral JG. A pilot study analyzing PSA, serum testosterone, lipid profile, body mass index and race in a small sample of patients with and without carcinoma of the prostate. Prostate Cancer Prostatic Dis. 2001;4(2):101-105 (critics: no dietary factors were taken into account, only high BMI as a risk factor, none serum SHBG analysed: dehydrated persons have usually high SHBG, and thus high total testosterone, which is bound to it, but generally low active, bioavailable and free testosterone levels)


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


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

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

ALTERNATIVE EXPLANATIONS: The higher testosterone levels found in men with prostate cancer in some investigations may be explained by

I. By the endogenous production of testosterone by the prostate cancer tumor ⇒ the higher testosterone would then be a consequence and marker of prostate cancer and not a cause or favoring factor

An in vitro study that demonstrates the production of testosterone by the (androgen independent) prostate cancer cells

In vivo studies that show that androgen levels cannot be suppressed to zero despite high dosing with LH antagonists in many men with metastatic prostate cancer, suggesting that the tumor itself could secrete testosterone

II. Dietary factors: The consumption of foods that favor the development of prostate cancer could also help produce higher free testosterone levels

Studies where the consumption of high amounts of protein and saturated fat such as milk products and meat increased testosterone levels

Milk or meat intake may increase the risk of prostate cancer (in fact the increased risk may disappear if the vegetable intake which is lower in meat eaters is taken into account)

Link between meat, milk and/or protein intake, and prostate cancer
Breast cancer: no increase in risk with estrogen therapy

Studies where estrogen treatment of women with previous breast cancer reduced the breast cancer recurrence and increased longevity/survival time


Studies where the use of HRT reduced the recurrence of breast cancer in women with previous breast cancer


Studies where the use of HRT (pill, conjugated estogens, estradiol patch, ..) did not increase the risk of breast cancer in women with previous breast cancer


Estrogen with non–bioidentical medroxyprogesterone acetate therapy after breast cancer: increases breast cancer recurrence

122. (30) Holmberg L, Anderson H; HABITS steering and data monitoring committees. HABITS (hormonal replacement therapy after breast cancer--is it safe?), a randomised comparison: trial stopped. Lancet. 2004 Feb 7;363(9407):453-5. Uppsala University, Sweden

Medroxyprogesterone acetate doubles the proliferation of breast epithelial cells, while bioidentical progesterone considerably reduce it

123. (31) 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. Department of Physiology, Michigan State University, East Lansing 48824, USA (n = 86 postmenopausal women)


Lower incidence of overall, breast and prostate cancer in women and men treated with a combination of anti-aging therapies, including hormone therapies

The example of vitamin D, where a serum level above the upper reference limit is better for health.

Exemple de la vitamine D où un taux au-dessus de la valeur de référence supérieure semble mieux pour la santé.