WELLNESS FOR LIFE
HEALTHY AND STRONG FROM THE INSIDE OUT

Testosterone Therapy: Health Risks Associated with Low-T & Evidence for Therapy

A decrease in Testosterone is associated with an increase in all-cause mortality and cardiovascular risk.

Araujo, A. Dixon, J.M., Suarez, E.A., Murad, M.H., Guey, L.T. & Wittert, G.J. (2011). Endogenous testosterone and mortality in men: A systematic review and meta-analysis. The Journal of Clinical Endocrinology & Metabolism, 96(10), 3007–3019, https://doi.org/10.1210/jc.2011-1137

Corona, G., Monami, M., Rastrelli, G., Aversa, A., Tishova, Y., Saad, F., Lenzi, A., Forti, G., Mannucci, E., & Maggi, M. (2011). Testosterone and metabolic syndrome: A meta-analysis study. Journal of Sexual Medicine, 8(1), 272-83. https://doi.org/10.1111/j.1743-6109.2010.01991

Khaw, K. T., Dowsett, M., Folkerd, E., Bingham, S., Wareham, N., Luben, R., Welch, A., & Day, N. (2007). 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, 116(23), 2694–2701. https://doi.org/10.1161/CIRCULATIONAHA.107

Laughlin, G. A., Barrett-Connor, E., & Bergstrom, J. (2008). Low serum testosterone and mortality in older men. The Journal of Clinical Endocrinology and Metabolism, 93(1), 68–75. https://doi.org/10.1210/jc.2007-1792

Traish, A. M., Saad, F., Feeley, R. J., & Guay, A. (2009). The dark side of testosterone deficiency: III. Cardiovascular disease. Journal of Andrology, 30(5), 477–494. https://doi.org/10.2164/jandrol.108.007245

A decrease in Testosterone is associated with an increase in overall healthcare costs.

Moskovic, D. J., Araujo, A. B., Lipshultz, L. I., & Khera, M. (2013). The 20-year public health impact and direct cost of testosterone deficiency in U.S. men. The Journal of Sexual Medicine, 10(2), 562–569. https://doi.org/10.1111/j.1743-6109.2012.02944

A decrease in Testosterone is associated with osteoporotic fractures and sarcopenia (muscle wasting).

Harman, S. M., Metter, E. J., Tobin, J. D., Pearson, J., Blackman, M. R., & Baltimore Longitudinal Study of Aging (2001). Longitudinal effects of aging on serum total and free testosterone levels in healthy men. Baltimore Longitudinal Study of Aging. The Journal of clinical endocrinology and metabolism, 86(2), 724–731. https://doi.org/10.1210/jcem.86.2.7219

A decrease in Testosterone is associated with erectile dysfunction.

Novo, S., Iacona, R., Bonomo, V., Evola, V., Corrado, E., Di Piazza, M., Novo, G., & Pavone, C. (2015). Erectile dysfunction is associated with low total serum testosterone levels and impaired flow-mediated vasodilation in intermediate risk men according to the Framingham risk score. Atherosclerosis, 238(2), 415–419. https://doi.org/10.1016/j.atherosclerosis.2014.12.007

A decrease in Testosterone is associated with cognitive decline.

Cai, Z., & Li, H. (2020). An updated review: Androgens and cognitive impairment in older men. Frontiers in Endocrinology, 11, 586909. https://doi.org/10.3389/fendo.2020.586909

Evidence basis for testosterone replacement therapy (TRT).

Testosterone improves erectile dysfunction.

Cunningham, G. R., Stephens-Shields, A. J., Rosen, R. C., Wang, C., Bhasin, S., Matsumoto, A. M., Parsons, J. K., Gill, T. M., Molitch, M. E., Farrar, J. T., Cella, D., Barrett-Connor, E., Cauley, J. A., Cifelli, D., Crandall, J. P., Ensrud, K. E., Gallagher, L., Zeldow, B., Lewis, C. E., Pahor, M., … Snyder, P. J. (2016). Testosterone treatment and sexual function in older men with low testosterone levels. The Journal of Clinical Endocrinology and Metabolism, 101(8), 3096–3104. https://doi.org/10.1210/jc.2016-1645

Rizk, P. J., Kohn, T. P., Pastuszak, A. W., & Khera, M. (2017). Testosterone therapy improves erectile function and libido in hypogonadal men. Current Opinion in Urology, 27(6), 511–515. https://doi.org/10.1097/MOU.0000000000000442

Testosterone reduces cognitive decline and improves cognitive function.

Bassil, N., Alkaade, S., & Morley, J. E. (2009). The benefits and risks of testosterone replacement therapy: a review. Therapeutics and Clinical Risk Management, 5(3), 427–448. https://doi.org/10.2147/tcrm.s3025

Bianchi V. E. (2022). Impact of testosterone on Alzheimer's disease. The World Journal of Men's Health, 40(2), 243–256. https://doi.org/10.5534/wjmh.210175

Testosterone protects against and improves bone mineral density loss.

Amory, J. K., Watts, N. B., Easley, K. A., Sutton, P. R., Anawalt, B. D., Matsumoto, A. M., Bremner, W. J., & Tenover, J. L. (2004). Exogenous testosterone or testosterone with finasteride increases bone mineral density in older men with low serum testosterone. The Journal of Clinical Endocrinology and Metabolism, 89(2), 503–510. https://doi.org/10.1210/jc.2003-031110

Yassin, A., Almehmadi, Y., Saad, F., Doros, G., & Gooren, L. (2016). Effects of intermission and resumption of long-term testosterone replacement therapy on body weight and metabolic parameters in hypogonadal in middle-aged and elderly men. Clinical Endocrinology, 84(1), 107–114. https://doi.org/10.1111/cen.12936

Testosterone improves insulin resistance and can reverse type II diabetes.

Cai, X., Tian, Y., Wu, T., Cao, C. X., Li, H., & Wang, K. J. (2014). Metabolic effects of testosterone replacement therapy on hypogonadal men with type 2 diabetes mellitus: a systematic review and meta-analysis of randomized controlled trials. Asian Journal of Andrology, 16(1), 146–152. https://doi.org/10.4103/1008-682X.122346

Wittert, G., Bracken, K., Robledo, K. P., Grossmann, M., Yeap, B. B., Handelsman, D. J., Stuckey, B., Conway, A., Inder, W., McLachlan, R., Allan, C., Jesudason, D., Fui, M. N. T., Hague, W., Jenkins, A., Daniel, M., Gebski, V., & Keech, A. (2021). Testosterone treatment to prevent or revert type 2 diabetes in men enrolled in a lifestyle program (T4DM): a randomised, double-blind, placebo-controlled, 2-year, phase 3b trial. The lancet. Diabetes & Endocrinology, 9(1), 32–45. https://doi.org/10.1016/S2213-8587(20)30367-3

Testosterone reduces cardiovascular risks.

Corona, G., Maseroli, E., Rastrelli, G., Isidori, A. M., Sforza, A., Mannucci, E., & Maggi, M. (2014). Cardiovascular risk associated with testosterone-boosting medications: a systematic review and meta-analysis. Expert Opinion on Drug Safety, 13(10), 1327–1351. https://doi.org/10.1517/14740338.2014.950653

Morgentaler, A., Miner, M. M., Caliber, M., Guay, A. T., Khera, M., & Traish, A. M. (2015). Testosterone therapy and cardiovascular risk: advances and controversies. Mayo Clinic Proceedings, 90(2), 224–251. https://doi.org/10.1016/j.mayocp.2014.10.011

Testosterone improves mood.

Snyder, P. J., Bhasin, S., Cunningham, G. R., Matsumoto, A. M., Stephens-Shields, A. J., Cauley, J. A., Gill, T. M., Barrett-Connor, E., Swerdloff, R. S., Wang, C., Ensrud, K. E., Lewis, C. E., Farrar, J. T., Cella, D., Rosen, R. C., Pahor, M., Crandall, J. P., Molitch, M. E., Cifelli, D.,… Dougar, D.(2016). Effects of testosterone treatment in older men. The New England Journal of Medicine, 374(7), 611–624. https://doi.org/10.1056/NEJMoa1506119

Testosterone does not increase or worsen atherosclerosis.

Basaria, S., Harman, S. M., Travison, T. G., Hodis, H., Tsitouras, P., Budoff, M., Pencina, K. M., Vita, J., Dzekov, C., Mazer, N. A., Coviello, A. D., Knapp, P. E., Hally, K., Pinjic, E., Yan, M., Storer, T. W., & Bhasin, S. (2015). Effects of testosterone administration for 3 years on subclinical atherosclerosis progression in older men with low or low-normal testosterone levels: A randomized clinical trial. JAMA, 314(6), 570–581. https://doi.org/10.1001/jama.2015.8881

Testosterone improves coronary artery disease.

English, K. M., Steeds, R. P., Jones, T. H., Diver, M. J., & Channer, K. S. (2000). Low-dose transdermal testosterone therapy improves angina threshold in men with chronic stable angina: A randomized, double-blind, placebo-controlled study. Circulation, 102(16), 1906–1911. https://doi.org/10.1161/01.cir.102.16.1906

Sharma, R., Oni, O. A., Gupta, K., Chen, G., Sharma, M., Dawn, B., Sharma, R., Parashara, D., Savin, V. J., Ambrose, J. A., & Barua, R. S. (2015). Normalization of testosterone level is associated with reduced incidence of myocardial infarction and mortality in men. European Heart Journal, 36(40), 2706–2715. https://doi.org/10.1093/eurheartj/ehv346

Webb, C. M., McNeill, J. G., Hayward, C. S., de Zeigler, D., & Collins, P. (1999). Effects of testosterone on coronary vasomotor regulation in men with coronary heart disease. Circulation, 100(16), 1690–1696. https://doi.org/10.1161/01.cir.100.16.1690

Despite the 2015 FDA Black Box warning on testosterone, there is insufficient evidence that testosterone is associated with cardiovascular events.

Miner, M., Morgentaler, A., Khera, M., & Traish, A.M. (2018). The state of testosterone therapy since the FDA's 2015 labelling changes: Indications and cardiovascular risk. Clinical Endocrinology, 89(1), 3-10. https://doi.org/10.1111/cen.13589

Testosterone therapy has no adverse effects on the prostate including cancer risks.

Barqawi, A., & Crawford, E. D. (2006). Testosterone replacement therapy and the risk of prostate cancer. Is there a link?. International Journal of Impotence Research, 18(4), 323–328. https://doi.org/10.1038/sj.ijir.3901418

Bassil, N., Alkaade, S., & Morley, J. E. (2009). The benefits and risks of testosterone replacement therapy: a review. Therapeutics and Clinical Risk Management, 5(3), 427–448. https://doi.org/10.2147/tcrm.s3025

Loeb, S., Folkvaljon, Y., Damber, J. E., Alukal, J., Lambe, M., & Stattin, P. (2017). Testosterone replacement therapy and risk of favorable and aggressive prostate cancer. Journal of Clinical Oncology, 35(13), 1430–1436. https://doi.org/10.1200/JCO.2016.69.5304

Morgentaler A. (2006). Testosterone and prostate cancer: A historical perspective on a modern myth. European Urology, 50(5), 935–939. https://doi.org/10.1016/j.eururo.2006.06.034

Ramasamy, R., Fisher, E. S., & Schlegel, P. N. (2012). Testosterone replacement and prostate cancer. Journal of the Urological Society of India, 28(2), 123–128. https://doi.org/10.4103/0970-1591.98449

Rhoden, E. L., & Morgentaler, A. (2004). Risks of testosterone-replacement therapy and recommendations for monitoring. The New England Journal of Medicine, 350(5), 482–492. https://doi.org/10.1056/NEJMra022251

What, Why, and How Do We Test?

Blood testing (serum):

Complete Blood Count (CBC): Provides indicators of anemia and infection as well as inflammation.

Comprehensive Metabolic Panel (CMP): Provides indicators of kidney and liver function as well as chemical and metabolic markers of health.

LIPID Panel: Lipid levels, particularly LDL and triglycerides indicate cardiac risk factors when elevated. Conversely low HDL are a risk factor for low testosterone.

Total/Free Testosterone: Only free testosterone is bioavailable.

Sex Hormone Binding Globulin (SHBG): Higher than average levels of SHBG can indicate inadequate circulating levels of bioavailable testosterone.

Dihydrotestosterone (DHT): Testosterone is converted to DHT via 5-alpha reductase. Adequate levels of DHT are needed for libido, sexual function, and muscle tone. High levels can lead to abnormal hair growth or loss (baldness), BPH or prostate cancer.

Dehydroepiandrosterone sulfate (DHEA-S): DHEA is converted by several pathways to different forms of testosterone or estrogen. DHEA is protective against cancer, diabetes, obesity, high cholesterol, heart disease, and autoimmune diseases.

Estradiol: Testosterone is converted to different forms of estrogen via aromatization. High levels of estrogen may indicate a dysfunction in conversion pathways.

Luteinizing hormone (LH): Low levels may indicate pituitary dysfunction.

Follicle stimulating hormone (FSH): Low levels may indicate pituitary dysfunction.

Prolactin: High levels are associated with low testosterone and low levels may indicate presence of a prolactinoma.

Prostate Specific Antigen (PSA): A baseline PSA level is established as marker for prostate health.

Micronutrients: Vitamin D 25-hydroxy and B-12 deficiency are frequently underdiagnosed. Low levels of these nutrients are associated with fatigue, poor stamina, mental fog, and general poor health.

Other Tests Ordered Based on Therapy Type, Symptoms & Serum Levels.

- **Additional hormones** including but not limited to progesterone, insulin, cortisol, melatonin and pregnanolone.
- **Additional inflammatory, autoimmune or deficiency markers** including but not limited to high sensitivity c-reactive protein, homocysteine, Methylmalonic Acid (MMA), antinuclear antibody (ANA), A1C, and thyroid peroxidase antibodies (TPO).
- **24-hour urine testing:** Testing looks at evidence of the different phases of hormone conversion/detoxification processes through hormone metabolites. Additionally, this test is the gold standard for kidney function.
- **Saliva Testing:** Cortisol Awaking Response, Cortisol diurnal pattern, monitoring for transdermal hormone replacement.
- **Dried urine test:** Organic Acid Test for hormone metabolite indicators of serum levels as well as detoxification and conversion pathway health.
- **Genetic testing:**