Kivessyövän sairastaneen potilaan hypogonadismin hoito

Satu Vehkavaara
oyl, dosentti
HYKS Jorvin sairaala
endokrinologian pkl

Sidonnaisuudet:

Olen toiminut asiantuntijatehtävissä tai luennoitsijana
Sanofin, Novo-Nordiskin ja Novartiksen koulutustilaisuuksissa sekä osallistunut
Ipsenin, Sanofin, Novartiksen ja Novo Nordiskin järjestämiin kongresseihin

Luento koostuu:

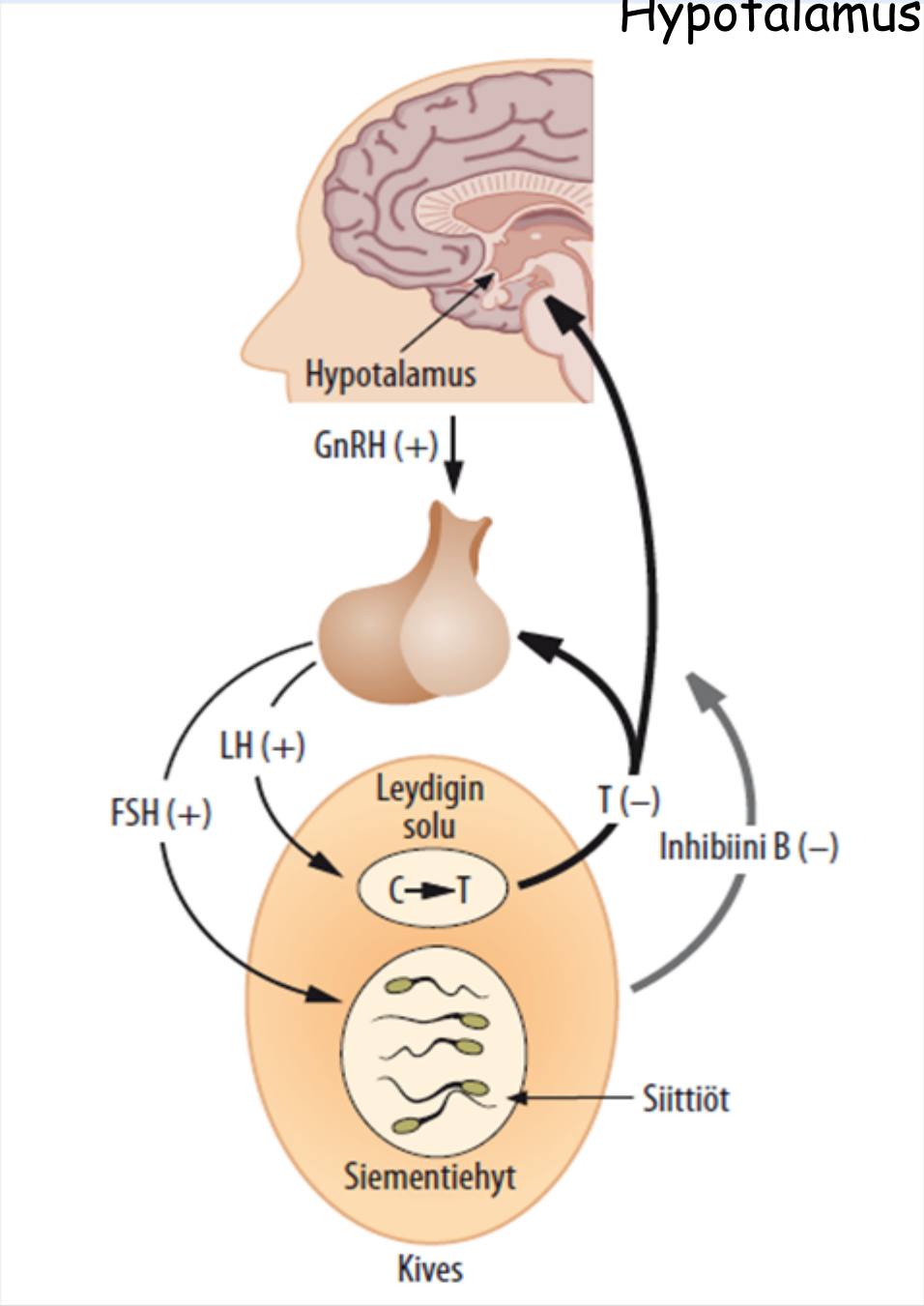
Säätelyjärjestelmä

Viitearvot ja hypogonadismin diagnostiikka

Kansainväliset suositukset hoidosta ja seurannasta

Hoidon monitorointi

Hypotalamus-aivolisäke-kivesakseli



Testosteroni vaikuttaa kohde-elimiinsä joko suoraan tai muuttuen 5a-reduktaasin vaikutuksesta dihydrotestosteroniksi tai aromataasin vaikutuksesta estradioliksi.

S-Testosteronin viitearvot miehillä

- HUSLAB 10 – 38 nmol/L (LC-MS/MS)
- NORDLAB 10 – 38 nmol/L (LC-MS/MS)
- FIMLAB 10 – 38 nmol/L (LC-MS/MS)
- ISLAB 10 – 38 nmol/L (LC-MS/MS)
- TYKSLAB 10 – ***33*** nmol/L (**uutos+RIA**)

- Näytteenotto: aamulla korkeimmillaan (vrk-vaihtelu)

- Endocrine Society tulkintarajat
- (J Clin Endoc Metab 2010, 95:2536-59)

Normaali	**yli 10 nmol/L**
Epävarma	**8– 10 nmol/L**
Alentunut (poikkeava)	**alle 8 nmol/L**

Testosterone Therapy in Men with Androgen Deficiency Syndromes: An Endocrine Society Clinical Practice Guideline

Shalender Bhasin, Glenn R. Cunningham, Frances J. Hayes, Alvin M. Matsumoto, Peter J. Snyder, Ronald S. Swerdloff, and Victor M. Montori

Anamneesi ja status

↓

Testosteroni (aamulla)

↓

Matala

↓

Poissulje akuutti sairaus, lääkevaikutus ja aliravitsemus (paino)
Tarkista testosteroni uudestaan (tarvittaessa SHBG) + LH+FSH
Jos perheenlisäystoive, siemennesteanalyysi

↓

Matala testosteroni, matala/normaali LH+FSH (sekundaarinen hypogonadismi)

↓

Tarkista prolaktiini ja harkinnan mukaan muut aivolisäkehormonit ja sellan MRI, jos testo < 5 nmol/l

↓

Matala testosteroni, korkea LH+FSH (primaarinen hypogonadismi)

↓

Kromosomianalyysi (Klinefelter)

↑

Normaali testosteroni, LH ja FSH

↑

Seurantalinja

J Clin Endocrinol Metab, June 2010, 95(6):2536–2559

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TABLE 1. Symptoms and signs suggestive of androgen deficiency in men

A. More specific symptoms and signs
- Incomplete or delayed sexual development, eunuchoidism
- Reduced sexual desire (libido) and activity
- Decreased spontaneous erections
- Breast discomfort, gynecomastia
- Loss of body (axillary and pubic) hair, reduced shaving
- Very small (especially <5 ml) or shrinking testes
- Inability to father children, low or zero sperm count
- Height loss, low trauma fracture, low bone mineral density
- Hot flushes, sweats

B. Other less specific symptoms and signs
- Decreased energy, motivation, initiative, and self-confidence
- Feeling sad or blue, depressed mood, dysthymia
- Poor concentration and memory
- Sleep disturbance, increased sleepiness
- Mild anemia (normochromic, normocytic, in the female range)
- Reduced muscle bulk and strength
- Increased body fat, body mass index
- Diminished physical or work performance

TABLE 2. Conditions associated with alterations in SHBG concentrations

Conditions associated with decreased SHBG concentrations
- Moderate obesity[a]
- Nephrotic syndrome[a]
- Hypothyroidism
- Use of glucocorticoids, progestins, and androgenic steroids[a]
- Acromegaly
- Diabetes mellitus[a]

Conditions associated with increased SHBG concentrations
- Aging[a]
- Hepatic cirrhosis and hepatitis[a]
- Hyperthyroidism
- Use of anticonvulsants[a]
- Use of estrogens
- HIV disease

[a] Particularly common conditions associated with alterations in SHBG concentrations.

J Clin Endocrinol Metab, June 2010, 95(6):2536–2559

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TABLE 3. Conditions in which there is a high prevalence of low testosterone levels and for which we suggest measurement of serum testosterone levels

Sellar mass, radiation to the sellar region, or other diseases of the sellar region
Treatment with medications that affect testosterone production or metabolism, such as glucocorticoids and opioids
HIV-associated weight loss
End-stage renal disease and maintenance hemodialysis
Moderate to severe chronic obstructive lung disease
Infertility
Osteoporosis or low trauma fracture, especially in a young man
Type 2 diabetes mellitus

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Lopeta hoito/älä aloita, jos todetaan

eturauhassyöpä
rintasyöpä
PSA koholla tai vaikeat virtsaoireet
Hkr > 50% (54%)
Sydämen vajaatoiminta (dekompensaatio)
Vaikea uniapnea
Maksakasvain

J Clin Endocrinol Metab, June 2010, 95(6):2536–2559

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Hoidon haittavaikutuksia (vahva evidenssi)
Erytrosytoosi (lopeta hoito, jos Hkr >54%)
Akne ja ihon rasvoittuminen
Piilevän eturauhassyövän löytyminen
Infertiliteetti

Hoidon haittavaikutuksia (heikko evidenssi)
Gynekomastia
Miestyyppinen kaljuuntuminen
Rintasyövän kasvun kiihtyminen
Uniapnean vaikeutuminen

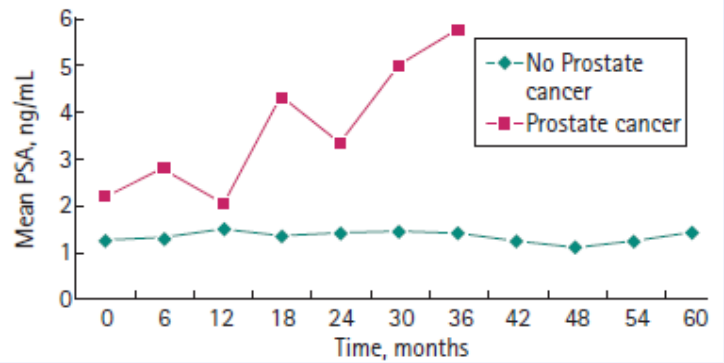
Pistos- ja geelihoitoon liittyvät ongelmat

J Clin Endocrinol Metab, June 2010, 95(6):2536–2559

BJUI
BJU INTERNATIONAL

Prostate-specific antigen changes and prostate cancer in hypogonadal men treated with testosterone replacement therapy

Robert M. Coward, Jay Simhan and Culley C. Carson III
Division of Urologic Surgery, The University of North Carolina, Chapel Hill, NC, USA



S-PSA totaali yli 67-v miehillä < 6.2 µg/l (alle 56-v < 3.3 ug/l)

PSA nousu hoidon aikana enintään 1.4 µg/l/12 kk tai
nousunopeus enintään 0.4 µg/l/vuosi (edellyttää 2 vuoden PSA-seurantaa)

Urologille myös, jos todetaan poikkeava palpaatiolöydös tai
virtsaoireet vaikeutuvat.

HOIDON MONITOROINTI

Lihakseen pistettävät valmisteet:
Sustanon®Nebido®
Testo ½-välissä 15-25 nmol/l ja
ennen seuraavaa pistosta
viitealueen alarajalla.

Iholle levitettävät geelit:
Tostran® Testim®Testogel®
50 mg →testo 12.7 nmol/l
100 mg → testo 21.3 nmol/l

Suun kautta otettava kapseli:
Panteston®
Huippupitoisuus 4-5 h

Hoidon alussa, 3-6 kk ja jatkossa vuosittain:
testosteronipitoisuus
Hkr
PSA

FERTILITEETIN PALAUTTAMINEN

Kiveksen sisäisen testosteroni-pitoisuuden suurentaminen LH-vaikutusta omaavalla valmisteella

Pregnyl (1500-3000 IU)x2/viikko

FSH-valmistetta riittävän FSH-pitoisuuden aikaansaamiseksi

Gonal-F (75-150) IU x 3/viikko

The NEW ENGLAND JOURNAL of MEDICINE

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Adverse Events Associated with Testosterone Administration

Shehzad Basaria, M.D., Andrea D. Coviello, M.D., Thomas G. Travison, Ph.D., Thomas W. Storer, Ph.D., Wildon R. Farwell, M.D., M.P.H., Alan M. Jette, Ph.D., Richard Eder, B.A., Sharon Tennstedt, Ph.D., Jagadish Ulloor, Ph.D., Anqi Zhang, Ph.D., Karen Choong, M.D., Kishore M. Lakshman, M.D., Norman A. Mazer, M.D., Ph.D., Renee Miciek, M.S., Joanne Krasnoff, Ph.D., Ayan Elmi, B.A., Philip E. Knapp, M.D., Brad Brooks, B.S., Erica Appleman, M.A., Sheetal Aggarwal, B.S., C.C.R.P., Geeta Bhasin, B.A., Leif Hede-Brierley, Ashmeet Bhatia, M.B., B.S., Lauren Collins, R.N.P., Nathan LeBrasseur, Ph.D., Louis D. Fiore, M.D., and Shalender Bhasin, M.D.

Keski-ikä 74-vuotta
Testosteronigeelihoito
testosteronipitoisuus 19.9 nmol/l

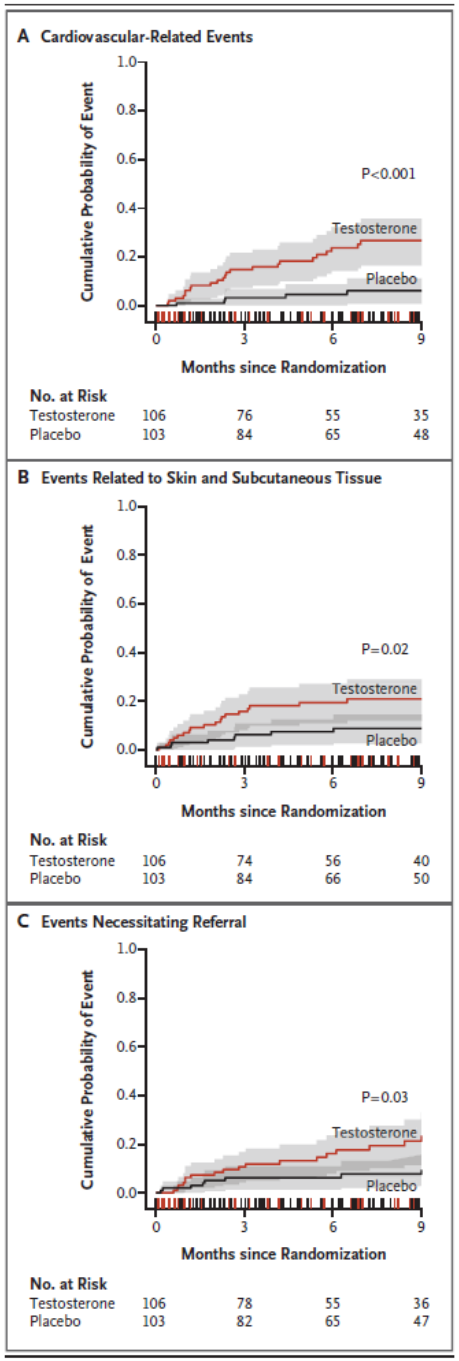


Figure 1. Time-to-Event Analysis of Adverse Events, According to Body System.

Kaplan–Meier estimates of the cumulative probability of incident cardiovascular-related adverse events (Panel A), events related to skin and subcutaneous tissue (Panel B), and events necessitating referral for medical evaluation (Panel C), from randomization to the end of the planned observation phase (9 months after randomization) are shown for the testosterone and placebo groups. The 95% confidence intervals are indicated by the shaded areas. The notches on the x axis show the distribution of censoring times before 9 months among participants in both groups. The P values were calculated from an unadjusted comparison of curves with the use of the log-rank test.

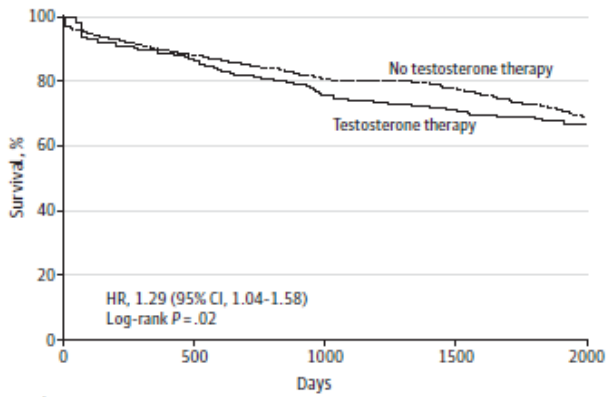
N Engl J Med 2010;363:109-22.

Original Investigation

Association of Testosterone Therapy With Mortality, Myocardial Infarction, and Stroke in Men With Low Testosterone Levels

Rebecca Vigen, MD, MSCS; Colin I. O'Donnell, MS; Anna E. Barón, PhD; Gary K. Grunwald, PhD; Thomas M. Maddox, MD, MSc; Steven M. Bradley, MD, MPH; Al Barqawi, MD; Glenn Woning, MD; Margaret E. Wierman, MD; Mary E. Plomondon, PhD; John S. Rumsfeld, MD, PhD; P. Michael Ho, MD, PhD

Figure 2. Kaplan-Meier Survival Curves With Testosterone Therapy Evaluated as a Time-Varying Covariate



No. at risk					
Testosterone therapy					
No	8709	5337	2897	918	206
Yes	0	439	500	233	61

CONCLUSIONS AND RELEVANCE Among a cohort of men in the VA health care system who underwent coronary angiography and had a low serum testosterone level, the use of testosterone therapy was associated with increased risk of adverse outcomes. These findings may inform the discussion about the potential risks of testosterone therapy.

JAMA. 2013;310(17):1829-1836. doi:10.1001/jama.2013.280386

Testosterone Treatment and Mortality in Men with Low Testosterone Levels

Molly M. Shores, Nicholas L. Smith, Christopher W. Forsberg, Bradley D. Anawalt, and Alvin M. Matsumoto

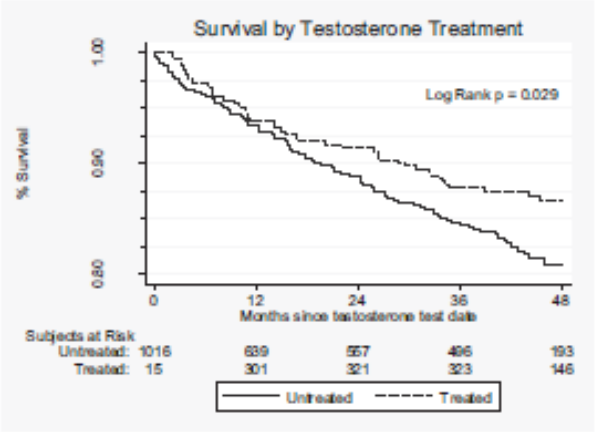


Fig. 1. Unadjusted Kaplan-Meier survival curves illustrate that testosterone-treated men had a longer survival time than untreated men ($P = 0.029$).

J Clin Endocrinol Metab, June 2012, 97(6):2050–2058

In Older Men an Optimal Plasma Testosterone Is Associated With Reduced All-Cause Mortality and Higher Dihydrotestosterone With Reduced Ischemic Heart Disease Mortality, While Estradiol Levels Do Not Predict Mortality

Bu B. Yeap, Helman Alfonso, S. A. Paul Chubb, David J. Handelsman, Graeme J. Hankey, Osvaldo P. Almeida, Jonathan Golledge, Paul E. Norman, and Leon Flicker

Table 1. Baseline Characteristics of the Study Population

Variable	Alive	Died	*P* Value
No. of participants	2716	974	
Age			
70–74 y	1191 (43.9)	204 (20.9)	
75–79 y	1167 (43.0)	419 (43.0)	<.001
80–84 y	310 (11.4)	273 (28.0)	<.001
≥85	48 (1.8)	78 (8.0)	<.001
Completed high school	1336 (49.2)	435 (44.7)	.016
Smoker			
Never	957 (35.2)	269 (27.6)	
Past	1635 (60.2)	624 (64.1)	<.001
Current	124 (4.6)	80 (8.2)	<.001
BMI ≥25 kg/m^2	1797 (66.2)	577 (60.1)	.001
WHR ≥0.90 cm	2318 (85.3)	813 (84.5)	.532
Hypertension	2091 (77.0)	763 (78.3)	.388
Dyslipidemia	1989 (73.2)	677 (69.5)	.026
Diabetes	402 (14.8)	164 (16.8)	.130
CVD	889 (34.0)	473 (49.9)	<.001
Cancer	238 (8.8)	136 (14.0)	<.001
Creatinine, μmol/L	91.6 ± 28.0	99.0 ± 39.8	<.001
Total T, nmol/L (ng/dL)	13.2 ± 4.8 (380 ± 138)	12.8 ± 5.1 (369 ± 147)	.013
Free T, pmol/L	187.8 ± 53.1	177.5 ± 57.4	<.001
DHT, nmol/L (ng/dL)	1.5 ± 0.7 (44 ± 20)	1.4 ± 0.7 (41 ± 20)	.002
E_2, pmol/L (pg/mL)	74.0 ± 29.0 (20.2 ± 7.9)	71.6 ± 29.3 (19.5 ± 8.0)	.022

Characteristics of the 3690 study participants at baseline, stratified according to whether men had died during the period of follow-up. Data are shown as number (%) for categorical variables or mean ± SD continuous variables. To convert T from nanomoles per liter to nanograms per deciliter, divide by 0.0347, to convert DHT from nanomoles per liter to nanograms per deciliter, divide by 0.0344, and to convert E_2 from picomoles per liter to picograms per milliliter divide by 3.671.

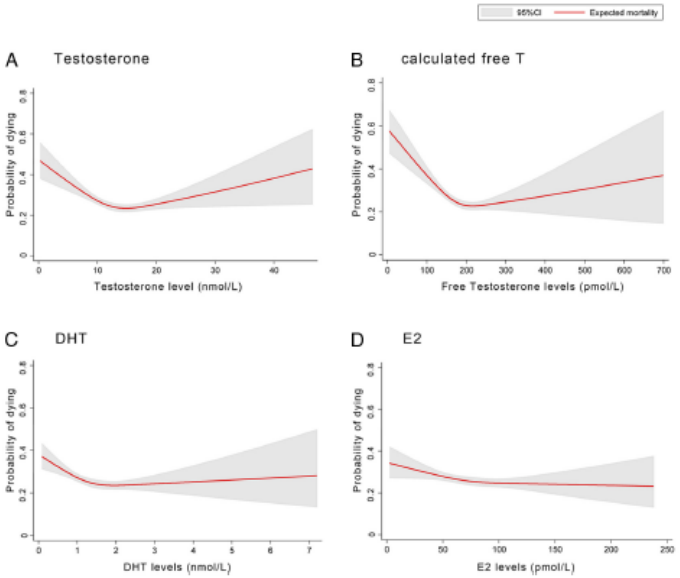


Figure 2. Probability of dying from any cause according to plasma levels of T (A), calculated free T (B), DHT (C) and estradiol (D) in 3690 community-dwelling men aged 70 to 89 years.

Optimaalinen testosteronipitoisuus välillä 9.8-15.8 nmol/l

Conclusions: Optimal androgen levels are a biomarker for survival because older men with midrange levels of T and DHT had the lowest death rates from any cause, whereas those with higher DHT had lower IHD mortality. Further investigations of the biological basis for these associations including randomized trials of T supplementation are needed. (*J Clin Endocrinol Metab* 99: E9–E18, 2014)

KIITOS !