남성갱년기 치료 Update

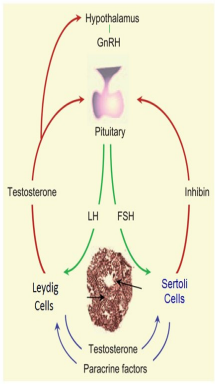
김 광 민
아주대병원

연수강좌

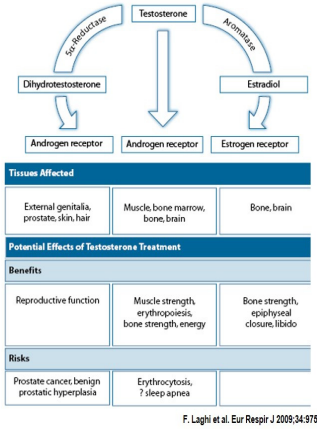
내용

- 어떤 경우에 남성호르몬 검사를 하나(남성호르몬 결핍 임상 증상) ?
- 증상은 전형적이지만 남성호르몬 수치가 약간 높다면? 반대의 경우는?
- 전립선 암과의 관련성은?
- 심혈관 질환과의 관련성은?
- 치료해서는 안 되는 경우는?
- 치료의 이점은?
- 치료 각각의 효과가 나타나는 시기는?
- 남성호르몬 치료제의 종류 및 선택 기준은?
- 남성호르몬 치료에서 장기작용 주사제의 경우 치료 간격 결정은?
- 남성갱년기 치료에서 검사 추적관리는?
- 어떤 증상과 혈액지표를 추적 검사시 확인해야 되나?
- 언제까지 해야 되나?

The Hypothalamus-Pituitary-Testes Axis of Testosterone production

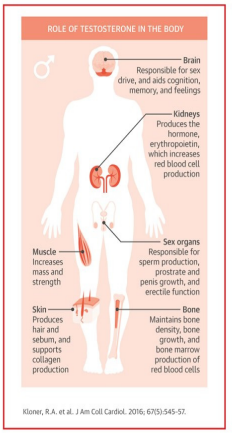


Mechanism of Action of Testosterone



F. Laghi et al. Eur Respir J 2009;34:975-996

The Effects of Testosterone on the Body



Kloner, R.A. et al. J Am Coll Cardiol. 2016; 67(5):545-57.

남성 노화에서 내분비 변화

< Massachusetts Male Aging Study : MMAS >
연령 : 40-70세, N = 1,156

1. 호르몬 감소
   총 테스토스테론 : ↓ 1.6 %/년
   유리 테스토스테론 : ↓ 2.8 %/년
   알부민 결합 테스토스테론 : ↓ 2.5%/년
   Androstenedione : ↓ 0.4%/yr
   Dehydroepiandrosterone : ↓ 1.4%/yr

2. 호르몬 증가
   성호르몬 결합 글로불린(SHBG) : ↑ 1.3 %/년
   황체화 호르몬 ↑ 0.9%/년, 난포자극호르몬 : ↑ 3.1%/년
   프로락틴 : ↑ 5.3%/년

3. 덜 건강한 남자(비만, 과도한 음주, 고혈압, 심혈관 질환, 당뇨 등):
   같은 감소율이나, 건강한 사람보다 10 - 15% 감소되어 있음

Feldman et al. J Clin Endocrinol Metab 2002;87:589-598

남성갱년기 정의

❋~~노화과정과 관련이 있으며~~, 특징적인 증상과 혈중 남성호르몬 결핍(젊은 건강한 성인 남성의 참고치 이하로)으로 특징 지워지는 임상적, 생화학적 증후군

❋ 삶의 질에 중대한 변화를 일으키며, 골, 지방조직, 근육, 조혈, 뇌, 피부 등 다중 기관의 기능에 안 좋은 영향

Aging Male. 2015 Mar;18(1):5-15

Testosterone deficiency

- Increasingly common problem with significant health implications
- Improving the diagnosis and management of TD in adult men should provide **somatic, sexual, and psychological benefits and subsequent improvements in quality of life**.

British Society for Sexual Medicine Guidelines on Adult Testosterone Deficiency, With Statements for UK Practice. J Sex Med 2017;14:1504e1523.

Clinical signs and symptoms suggestive of TD

Sexual
- Delayed puberty
- Small testes
- Infertility
- **Decreased sexual desire and activity**
- **Decreased frequency of sexual thoughts**
- **Erectile dysfunction**
- Delayed ejaculation
- Decreased volume of ejaculate
- Decreased or absent morning or night-time erections

Cardiometabolic
- **Increased BMI or obesity**
- **Visceral obesity**
- **Metabolic syndrome**

Physical
- Decreased body hair
- Gynecomastia
- **Decreased muscle mass and strength**
- Hot flushes or sweats
- Sleep disturbances
- **Fatigue**
- **Osteoporosis**, height loss, low trauma fractures

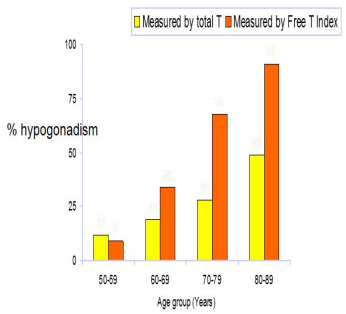
Psychological
- **Changes in mood** (eg, anger, irritability, sadness, depression)
- **Decreased well-being** or poor self-rated health
- **Decreased cognitive function** (including impaired concentration, verbal memory, and spatial performance)

Recommend the investigation of hypogonadism in men with the following conditions

- **Low libido** / Poor morning erections / Erectile dysfunction
- **Depressed mood / Fatigue / Decreased vitality / Cognitive impairment**
- Insulin resistance / Obesity / abdominal obesity / **Metabolic syndrome**
- Arterial hypertension / **Diabetes mellitus type 2**
- **Decreased muscle mass and strength**
- **Decreased bone mineral density and osteoporosis**
- **Use of glucocorticoids, opioids, antipsychotics**

Recommendations on the diagnosis, treatment and monitoring of hypogonadism in men. Aging Male. 2015 Mar;18(1):5-15.

Prevalence of hypogonadism in aging men Baltimore Longitudinal Study of Aging



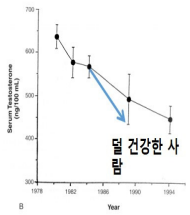
Harman et al. J Clin Endocrinol Metab 2001;86:724-731

남성호르몬 저하

- 복잡하고 다양한 병인
- 낮은 남성호로몬: **스트레스**, 노화, **질병**, 그리고 약물 복용 등과 관계
- 많은 임상 질병
  - 급성의 심한 질환
  - 만성 질환: 당뇨병, 심혈관 질환, 고혈압, hereditary hemochromatosis, HIV virus infection
  - 음주, 흡연 등의 **생활습관**
  - 영양 결핍 혹은 **비만**

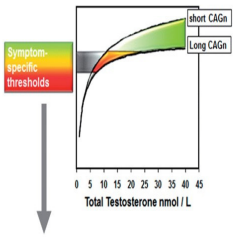
어떤 사람이 잘 생기나?

- 노화 : **건강한 노화가 아니라 여러 질병에 이환된 노화에서**
- 생활습관: 비만, 과도한 음주, **스트레스**
- **만성 질환**: 고혈압, 심혈관 질환, 당뇨, 만성폐쇄성폐질환 등

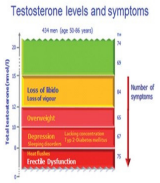


Metabolism 46:410,1997

Threshold continuum to hypogonadism



- ❖ 증상이 전형적인 저성선증에 해당
- ❖ 총 남성호르몬 수치가 다소 높더라도
- ❖ LH upper limit 이상
- ❖ SHBG upper limit 이상



Aging Male. 2015 Mar;18(1):5-15.

After 2015 guideline 에서 중요 내용

- 호르몬 수치 보다는 임상 증상이 중요
  --- 유전적 변이(CAG repeat), 수용체 민감도
- 비만과 당뇨병, 골다공증에서는 남성호르몬 선별검사가 필요
- Reversible Hypogonadism 개념
- 전립선 암에 대한 추적 검사 --- PSA, not mandatory for DRE

Testosterone Deficiency

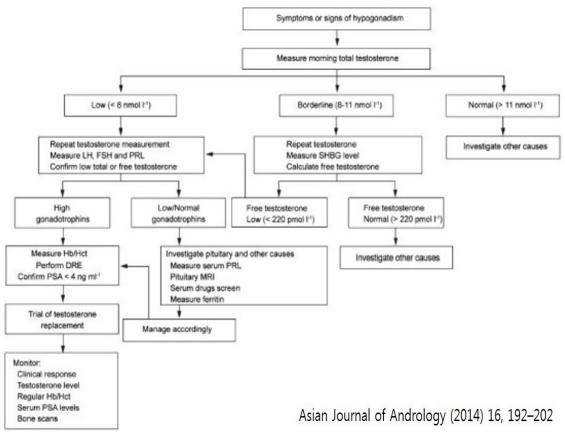
- **총 테스토스테론 농도: 350 ng/dl 이하 (WHO)**
  200 ng/dl 이하 (NIH)
  350 ng/dl 이하(우리나라)
- **FAI** **20(우리나라)**
- **cFT** **200 pmol/L(우리나라)**

10.4 nMol/L= 300 ng/dl **nMol/L x 28.8 = ng/dl**
pMol/L x 0.0288 = ng/dl

Committee of Endocrine Aspect, International Consultation on ED, WHO, 1999
대한 남성갱년기 학회,2004

EMAS Group proposed 11 nmol/L as a lower cut-off value for TT.
TT level < 12.1 nmol/L in three large cohorts comprising more than 10 000 men of various ages

Algorithm for the diagnosis and treatment of LOH



Asian Journal of Andrology (2014) 16, 192–202

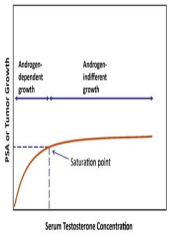
남성호르몬과 전립선 관계에 대한 오해

- Old fashion

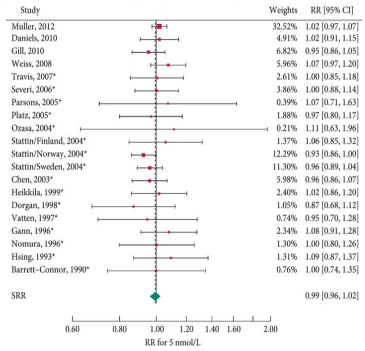
  "fuel for a fire and food for a hungry timor"

  PSA 증가 ? / 전립선 부피 증가 ? / 잠재적인 종양 apparent ?

- Present opinion : saturation theory



Serum testosterone and risk of prostate cancer (dose–response meta-analysis): a meta-analysis

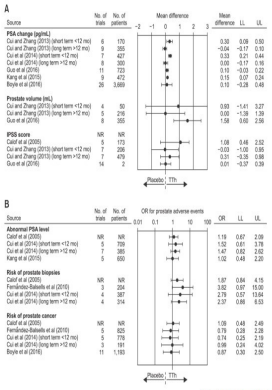


*: study included in EHPCCG pooled analysis

Heterogeneity: I^2 = 0% [0%; 19%]; Q = 12.20, df = 19 (p = 0.88)
Publication bias: Begg = 0.16 (p = 0.87); Egger = -0.79 (p = 0.17); Macaskill = -0.41 (p = 0.69)

BJU International 118(5) , pages 731-741, 24 FEB 2016

Prostate adverse events as derived from available meta-analyses of randomized controlled trials on the effect of testosterone therapy *vs*. placebo.



World J Mens Health. 2017 Aug;35(2):65-76.

Testosterone therapy and prostate cancer

- The use of TTh in the setting of CaP remains controversial due to a lack of definitive, appropriately powered prospective controlled studies.
- Available evidence supports the overall conclusion that **TTh in patients with a history of both treated or untreated CaP is both safe and effective, particularly in men with low risk malignancies.**
- TTh in men with a history of high-risk CaP is supported by small, retrospective studies that overall show no increased risk of CaP recurrence or progression in these men.
- In light of the available evidence, we recommend careful consideration of TTh in all men with an history of CaP while weighing the potential risks with the improvement in quality of life so clearly evidenced with TTh.

Transl Androl Urol 2016;5(6):909-920

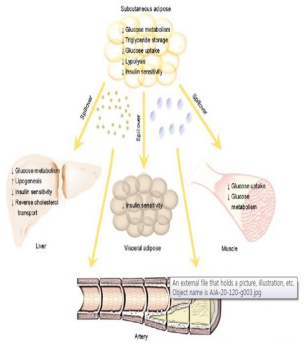
Testosterone therapy and prostate cancer

- The European Association of Urology uses level 3, grade B evidence to recommend that symptomatic men who have been surgically treated for localized prostate cancer and have no sign of active disease as evident by an undetectable PSA, a normal rectal exam, and an absence of metastatic disease, can be cautiously considered for TRT.
- This guideline also specifies that patients must have a history of low risk prostate cancer, including a preoperative PSA of less than 10 ng/mL, Gleason score of less than 8, and pathological stage T1–T2.
- Patients should not be started on TRT until a minimum of one year follow-up from their curative prostate cancer surgery.
- These guidelines do not comment on the use of TRT in the setting of active surveillance.

전립선 암 환자에서 남성호르몬 치료

- 전립선 암 방사선 치료 혹은 radical prostactomy 하고 난 후 1년 이후에는 PAS가 0.1 이하로 유지되면 치료.
- 치료 받지 않은 전립선 암에서 Gleason score 4-5일 때 남성호르몬 치료를 지속할 것인지 common sense ?

Potential detrimental metabolic actions of testosterone deficiency



Asian Journal of Andrology (2018) 20, 120–130

Endogenous androgens and cardiovascular disease

- T levels are consistently lower in men with CVD
- Low total and bioavailable T levels were associated with increased risk of aortic atherosclerosis in elderly men, independent of age, BMI, SHBG, T. Chol, HDL-Chol, DM, smoking, and alcohol intake.
- Link between hypogonadism and increased CAD

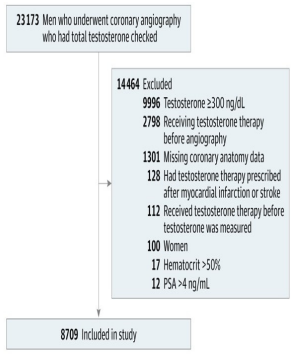
  --- Hypogonadism is thought to contribute to development of the metabolic syndrome , which increases CVD risk

남성호르몬과 심혈관 질환 : Debate ?

- Vigen et al, JAMA 2013 ;
  - 남성호르몬 치료가 심혈관 질환 위험 증가

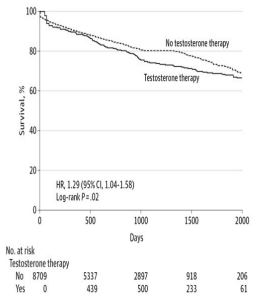
- 내인성 남성호르몬과 심혈관 질환, 사망률
- 남성호르몬 치료와 대사증후군, 당뇨병
- 남성호르몬 치료와 염증 인자

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



JAMA. 2013;310(17):1829-1836

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



1,587/7,486 (21.2%)

123/ 1223 (10.1%)

JAMA. 2013;310(17):1829-1836.

Limitation of this study

- 치료 기간 평균이 1년
- 환자의 17.6% ; 단지 1번의 남성호르몬 처방 받은 군이 포함

- Absolute risk

  보고한 내용 실제 계산

  19.9 % 1587/7486 = 21.2 % in no T Therapy,

  25.6 % 123/1223 = 10.1% in T Therapy.

- Large errors in data (2014년 5월)

  잘못된 사람들이 포함됨 --- 100 여명 이상이 제외 됨

  100명의 여성이 포함됨 --- 9%의 영향력

- 29 medical societies petitioned JAMA to retract study

Low testosterone is associated with increased mortality

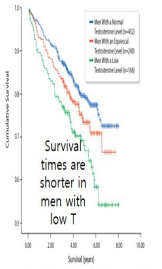


Figure 1. Unadjusted Kaplan-Meier survival curves for the three testosterone level groups. From Shores, Arch Intern Med. 2006.

- **Men with low testosterone levels** were found to have a **88% greater mortality risk due to all causes** than men with normal testosterone levels
- Similar findings in the EPIC-Norfolk and Rancho Bernardo studies

Shores MM et al. Arch Intern Med. 2006:166:1660-1665

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

Veterans Affairs (VA) Puget Sound Health Care System (M.M.S., N.L.S., C.W.F., A.M.M.), Seattle, Washington 98108; VA Epidemiologic Research and Information Center, (N.L.S., C.W.F.) and VA Geriatric Research, Education, and Clinic Center (A.M.M.), Seattle, Washington 98108; Departments of Psychiatry and Behavioral Sciences (M.M.S.), Epidemiology (N.L.S.), and Medicine (B.D.A., A.M.M.), University of Washington, Seattle, Washington 98105; and Group Health Research Institute (N.L.S.), Group Health Cooperative, Seattle, Washington 98101

Context: Low testosterone levels in men have been associated with increased mortality. However, the influence of testosterone treatment on mortality in men with low testosterone levels is not known.

Objective: The objective of the study was to examine the association between testosterone treatment and mortality in men with low testosterone levels.

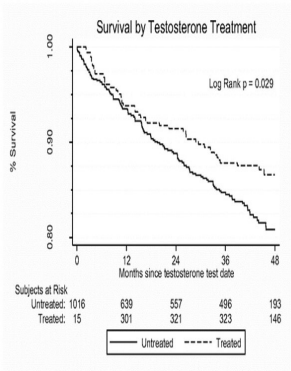
Design: This was an observational study of mortality in testosterone-treated compared with untreated men, assessed with time-varying, adjusted Cox proportional hazards regression models. Effect modification by age, diabetes, and coronary heart disease was tested a priori.

Setting: The study was conducted with a clinical database that included seven Northwest Veterans Affairs medical centers.

Patients: Patients included a cohort of 1031 male veterans, aged older than 40 yr, with low total testosterone [≤250 ng/dl (8.7 nmol/liter)] and no history of prostate cancer, assessed between January 2001 and December 2002 and followed up through the end of 2005.

J Clin Endocrinol Metab 97: 2050–2058, 2012

Testosterone-treated men had a longer survival time than untreated men



J Clin Endocrinol Metab 97: 2050–2058, 2012

JAMA Intern Med. 2017 Feb 21. doi: 10.1001/jamainternmed.2016.9548. [Epub ahead of print]

Association of Testosterone Replacement With Cardiovascular Outcomes Among Men With Androgen Deficiency.

Cheetham TC[1], Jee JF[2], Jacobsen SJ[3], Niu F[3], Sidney S[4], Quesenberry CP[4], VanDenEeden SK[4]

Author information

Abstract

IMPORTANCE: Controversy exists regarding the safety of testosterone replacement therapy (TRT) following recent reports of an increased risk of adverse cardiovascular events.

OBJECTIVE: To investigate the association between TRT and cardiovascular outcomes in men with androgen deficiency.

DESIGN, SETTING, AND PARTICIPANTS: A retrospective cohort study was conducted within an integrated health care delivery system. Men at least 40 years old with evidence of androgen deficiency either by a coded diagnosis and/or a morning serum total testosterone level of less than 300 ng/dL were included. The eligibility window was January 1, 1999, to December 31, 2010, with follow-up through December 31, 2012.

EXPOSURES: Any prescribed TRT given by injection, orally, or topically.

MAIN OUTCOMES AND MEASURES: The primary outcome was a composite of cardiovascular end points that included acute myocardial infarction (AMI), coronary revascularization, unstable angina, stroke, transient ischemic attack (TIA), and sudden cardiac death (SCD). Multivariable Cox proportional hazards models were used to investigate the association between TRT and cardiovascular outcomes. An inverse probability of treatment weight, propensity score methodology, was used to balance baseline characteristics.

RESULTS: The cohorts consisted of 6808 men (19.8%) ever dispensed testosterone (ever-TRT) (mean age, 58.4 years; 1.4% with prior cardiovascular events) and 35 527 men (80.2%) never dispensed testosterone (never-TRT) (mean age, 59.8 years; 2.0% with prior cardiovascular events). Median follow was 3.2 years (interquartile range [IQR], 1.7-6.6 years) in the never-TRT group vs 4.2 (IQR, 2.1-7.8) years in the ever-TRT group. The rates of the composite cardiovascular end point were 23.9 vs 16.9 per 1000 person-years in the never-TRT and ever-TRT groups, respectively. The adjusted hazard ratio (HR) for the composite cardiovascular end point in the ever-TRT group was 0.67 (95% CI, 0.62-0.73. Similar results were seen when the outcome was restricted to combined stroke events (stroke and TIA) (HR, 0.72; 95% CI, 0.62-0.84) and combined cardiac events (AMI, SCD, unstable angina, revascularization procedures) (HR, 0.66; 95% CI, 0.60-0.72).

CONCLUSIONS AND RELEVANCE: Among men with androgen deficiency, dispensed testosterone prescriptions were associated with a lower risk of cardiovascular outcomes over a median follow-up of 3.4 years.

CV outcomes by TRT

Individual CV Components	Summary Counts by Treatment Group: TRT-Never, CV Event, No.	TRT-Never, Event Rate, per 1000 Person-years[b]	TRT-Ever, CV Event, No.	TRT-Ever, Event Rate, per 1000 Person-years	Time Varying TRT With IPTW[a]: HR (LB-UB 95% CI)	P Value
Combined stroke	929	5.8	196	4.3	0.72 (0.62-0.84)	<.001
Stroke	501	3.1	95	2.1	0.64 (0.51-0.80)	<.001
TIA	428	2.7	101	2.2	0.82 (0.66-1.02)	.07
Cardiac event	2780	18.2	524	11.9	0.66 (0.59-0.72)	<.001
AMI	962	6.3	204	4.7	0.74 (0.63-0.86)	<.001
Revascularization	867	5.7	147	3.4	0.59 (0.49-0.70)	<.001
SCD	496	3.3	106	2.4	0.76 (0.61-0.92)	.009
Unstable angina	455	3.0	67	1.5	0.52 (0.41-0.68)	<.001
Death						
All-cause death	4088	23.1	864	16.7	0.72 (0.67-0.77)	<.001

Abbreviations: AMI, acute myocardial infarction; CV, cardiovascular; HR, hazard ratio; IPTW, inverse probability of treatment weight; LB, lower bound; revascularization, coronary artery bypass graft and percutaneous transluminal coronary angioplasty; SCD, sudden cardiac death; TIA, transient ischemic attack; TRT, testosterone replacement therapy; UB, upper bound.

[a] IPTW based on all patient characteristics included in Table 1 with doubly robust estimation, controlling for age, Kaiser Permanente region, index year, Elixhauser comorbidity score, congestive heart failure, dyslipidemia, diabetes, hypertension, prior cardiovascular events, and baseline testosterone.

[b] Event rates per 1000 person-years were calculated after applying IPTW.

JAMA 2017, Feb 21

Normalization of testosterone level is associated with reduced incidence of myocardial infarction and mortality in men

Rishi Sharma[1], Olurinde A. Oni[1], Kamal Gupta[2], Guoqing Chen[3], Mukut Sharma[1], Buddhadeb Dawn[2], Ram Sharma[1], Deepak Parashara[2,4], Virginia J. Savin[5], John A. Ambrose[6], and Rajat S. Barua[1,2,4]*

[1]Division of Cardiovascular Research, Kansas City VA Medical Center, Kansas City, MO, USA; [2]Division of Cardiovascular Diseases, University of Kansas Medical Center, Kansas City, KS, USA; [3]Division of Health Services Research, University of Kansas Medical Center, Kansas City, KS, USA; [4]Division of Cardiovascular Medicine, Kansas City VA Medical Center, 4801 E. Linwood Boulevard, Kansas City, MO 64128, USA; [5]Division of Nephrology, Kansas City VA Medical Center, Kansas City, MO, USA; and [6]Division of Cardiovascular Medicine, University of California San Francisco, Fresno, CA, USA

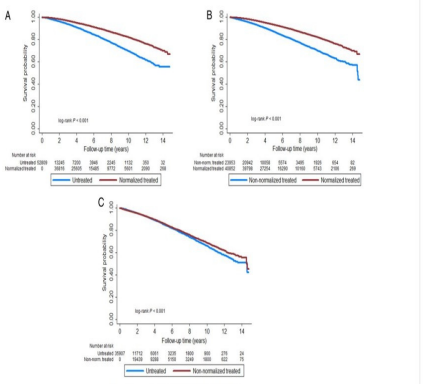
Received 2 June 2015, revised 1 July 2015, accepted 6 July 2015, online publish-ahead-of-print 6 August 2015

Aims There is a significant uncertainty regarding the effect of testosterone replacement therapy (TRT) on cardiovascular (CV) outcomes including myocardial infarction (MI) and stroke. The aim of this study was to examine the relationship between normalization of total testosterone (TT) after TRT and CV events as well as all-cause mortality in patients without previous history of MI and stroke.

Methods and results We retrospectively examined 83 010 male veterans with documented low TT levels. The subjects were categorized into (Gp1: TRT with resulting normalization of TT levels), (Gp2: TRT without normalization of TT levels) and (Gp3: Did not receive TRT). By utilizing propensity score-weighted Cox proportional hazard models, the association of TRT with all-cause mortality, MI, stroke, and a composite endpoint was compared between these groups. The all-cause mortality [hazard ratio (HR): 0.44, confidence interval (CI) 0.42–0.46], risk of MI (HR: 0.76, CI 0.63–0.93), and stroke (HR: 0.64, CI 0.43–0.96) were significantly lower in Gp1 ($n = 4393$ 1, median age = 66 years, mean follow-up = 6.2 years) vs. Gp3 ($n = 13$ 378, median age = 66 years, mean follow-up = 4.7 years) in propensity-matched cohort. Similarly, the all-cause mortality (HR: 0.53, CI 0.50–0.55), risk of MI (HR: 0.82, CI 0.71–0.95), and stroke (HR: 0.70, CI 0.51–0.96) were significantly lower in Gp1 vs. Gp2 ($n = 25$ 701, median age = 66 years, mean follow-up = 4.6 years). There was no difference in MI or stroke risk between Gp2 and Gp3.

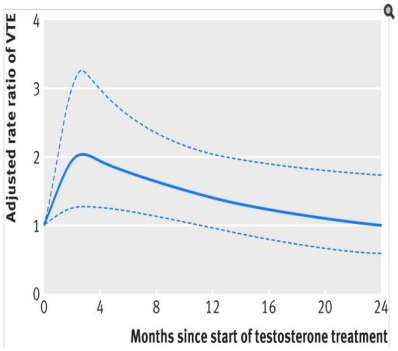
Conclusion In this large observational cohort with extended follow-up, normalization of TT levels after TRT was associated with a significant reduction in all-cause mortality, MI, and stroke.

The all-cause mortality among different propensity-matched study groups



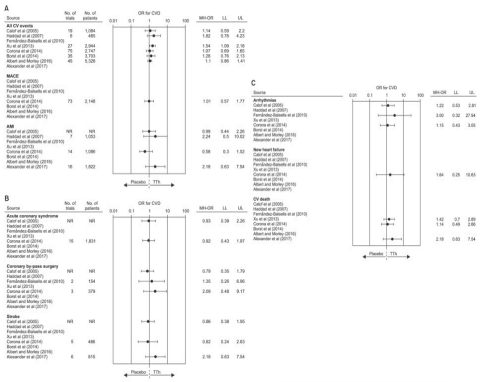
Eur Heart J. 2015;36(40):2706-2715.

Venous thromboembolism by time on current testosterone treatment



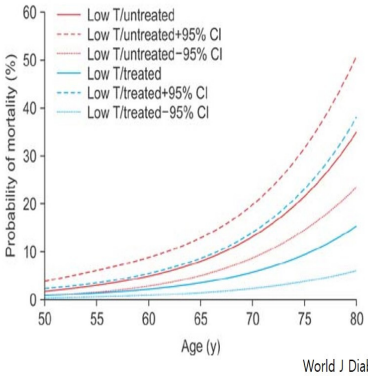
BMJ. 2016; 355: i5968.

Cardiovascular disease (CVD) events as derived from available meta-analyses of randomized controlled trials on the effect of testosterone therapy *vs.* placebo.



World J Mens Health. 2017 Aug;35(2):65-76.

Estimated mortality probability and 95% confidence intervals (CIs) from the fitted logistic regression.

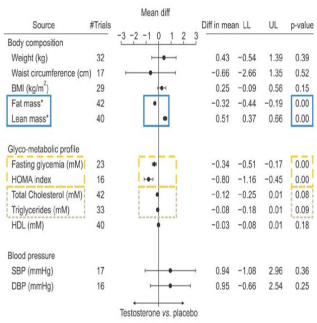


World J Diabetes 2017;8:104–11

남성갱년기를 치료해야 하는 이유

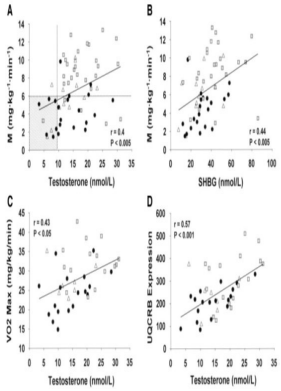
- 낮은 남성호르몬이 높은 사망률과 관련
- 대사증후군과 관련
- 치료시 대사증후군 인자 및 당뇨병 혈당 개선 효과
- 삶의 질 개선 효과

Meta-analysis of 59 randomized controlled trials of testosterone substitution in hypogonadism (3,029 treated *vs.* 2,049 controls) (mean duration=32.5 weeks)



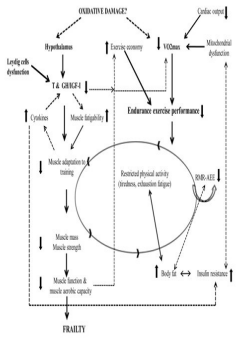
Eur J Endocrinol 2016;174:R99–116

Relationship Between Testosterone Levels, Insulin Sensitivity, and Mitochondrial Function in Men



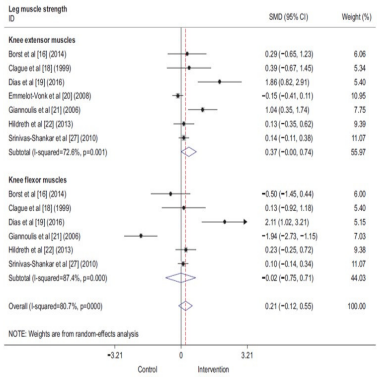
Diabetes Care 28:1636–1642, 2005

Aging-related detrimental changes in body systems that lead to physical function decline, with both anabolic hormone milieu and aerobic exercise capacity playing a key role



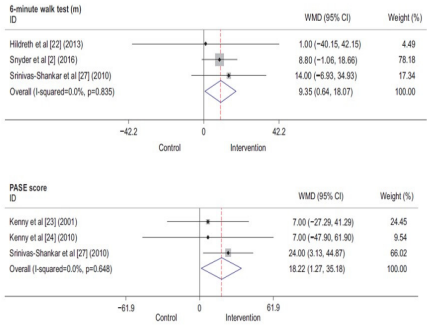
Endocrine Reviews, June 2012, 33(3):314–377

Leg muscle strength as derived from available randomized controlled trials on the effect of TRT *vs.* placebo.



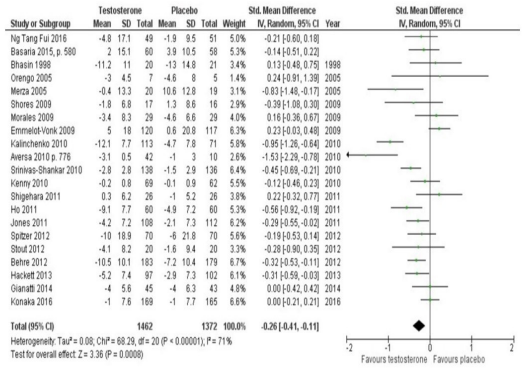
World J Men's Health 2018 May 36(2): 110-122

The 6-minute walk test and physical activity scale for the elderly (PASE) scale from available randomized controlled trials on the effect of TRT *vs.* placebo.



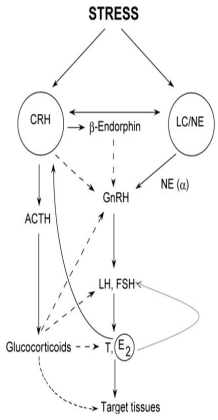
World J Men's Health 2018 May 36(2): 110-122

Meta-analysis of the effect of testosterone on quality of life



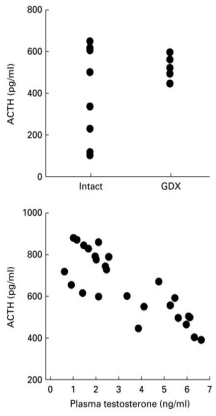
Jesse Elliott et al. BMJ Open 2017;7:e015284

The interactions between the stress system and the reproductive axis.



Annu. Rev. Physiol. 2005. 67:259–84

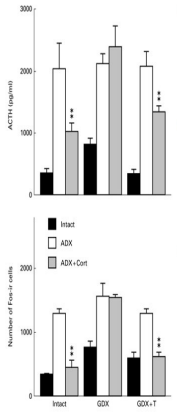
Functional Cross-Talk Between the Hypothalamic-Pituitary-Gonadal and -Adrenal Axes



- ACTH response to restraint stress in male rat
- Individual plasma testosterone concentration (ng/ml) in GDX, testosterone treated rats
- Variations in ACTH responses to stress are explained by individual differences in circulating testosterone concentrations
- ACTH responses in some intact males are comparable to GDX rats (top), indicating a minimal or threshold concentration of testosterone that is required for inhibition of the HPA axis

J of Neuroendocrinology, 2002(14), 506–513

Functional Cross-Talk Between the Hypothalamic-Pituitary-Gonadal and -Adrenal Axes



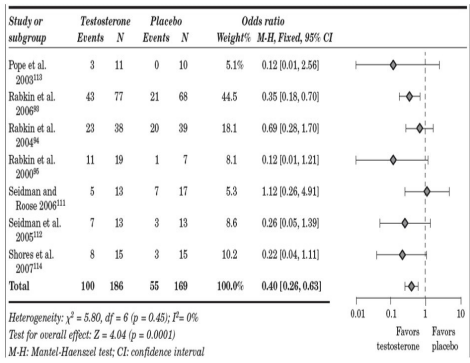
- ACTH and paraventricular nucleus (PVN) Fos responses to restraint stress in adrenal-intact, adrenalectomized (ADX) and ADX+corticosterone (Cort) replaced male rats as a function of gonadal status.
- Corticosterone replacement reversed the stimulatory effects of ADX on both stress-induced plasma ACTH and PVN Fos-immunoreactivity (ir) in rats with testis (Intact) and gonadectomized (GDX) rats replaced with testosterone (GDX+T), but not in GDX rats.
- This parallel response suggests that corticosterone and testosterone do not act independently on stress-induced ACTH release, but interact on stress-induced drive to the PVN motor neurones

J of Neuroendocrinology, 2002(14), 506–513

Functional Cross-Talk Between the Hypothalamic-Pituitary-Gonadal and -Adrenal Axes

- **The heterogeneity to individual differences in cortisol release patterns and HPA hyperactivity --- may very well depend on the gonadal axis**
- **The variability in testosterone accounts for individual differences in HPA responses to stress.**
- Individuals afflicted with depression show varying degrees of resistance to antidepressant treatment.
- Emerging clinical studies now show that a subset of depressed males are hypogonadal and that androgen replacement can reduce depressive symptomology

Testosterone and Depression: Systematic Review and Meta-Analysis



Study or subgroup	Testosterone Events	N	Placebo Events	N	Weight%	Odds ratio M-H, Fixed, 95% CI
Pope et al. 2003[113]	3	11	0	10	5.1%	0.12 [0.01, 2.56]
Rabkin et al. 2006[93]	43	77	21	68	44.5	0.35 [0.18, 0.70]
Rabkin et al. 2004[94]	23	38	20	39	18.1	0.69 [0.28, 1.70]
Rabkin et al. 2000[95]	11	19	1	7	8.1	0.12 [0.01, 1.21]
Seidman and Roose 2006[111]	5	13	7	17	5.3	1.12 [0.26, 4.91]
Seidman et al. 2005[112]	7	13	3	13	8.6	0.26 [0.05, 1.39]
Shores et al. 2007[114]	8	15	3	15	10.2	0.22 [0.04, 1.11]
Total	**100**	**186**	**55**	**169**	**100.0%**	**0.40 [0.26, 0.63]**

Heterogeneity: $\chi^2 = 5.80$, df = 6 (p = 0.45); I^2= 0%
Test for overall effect: Z = 4.04 (p = 0.0001)
M-H: Mantel-Haenszel test; CI: confidence interval

Journal of Psychiatric Practice,2009(15), 289-305

스트레스와 남성호르몬

- 스트레스가 남성호르몬 저하 유발
- 스트레스 반응 차이가 다른 이유에서 남성호르몬이 기여
- 우울증에서 항우울제에 대한 반응 차이가 있는 경우 남성호르몬 저하를 고려해야

남성호르몬 치료 이점

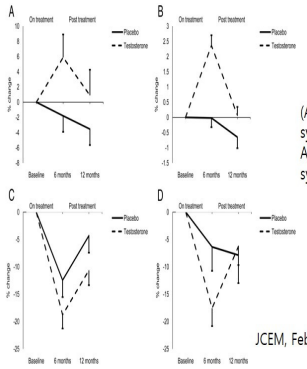
- 혈당, 당화혈색소, 수축기 혈압, 이완기 혈압, 지질 호전
- 체중 감소(근육량 증가 및 체지방 감소)
- 골밀도 증가
- 성기능 호전
- 우울감 호전
- vitality 증가
- 삶의 질 호전

- 수명 연장 ? / 심혈관 질환 예방 ?/ 인지 기능 호전?
- 전립선 암 치료에 도움 ? / 자가면역성 질환 ?

Testosterone therapy options

Formulation	Route of administration	Frequency of administration	Advantages	Disadvantages
Testosterone 1% and 2% gel available	Transdermal gel	Applied daily, requires dose titration	Fast onset; provide uniform and normal serum levels for 24 hours	Skin irritation at application site Potential for interpersonal transfer Non-compliance long term
Testosterone undecanoate	Oral capsules	Once or twice daily	Lymphatic absorption decrease liver involvement	Levels fluctuate Daily or twice-daily commitment Must be taken with food
Testosterone undecanoate	Intramuscular injection	Every 10 - 14 wk adjusted to maintain trough testosterone level > 12 nmol/L	Steady-state levels Lower frequency of administration improves compliance	Long duration of action prevents drug withdrawal in the event of adverse side effects
Testosterone enanthate	Intramuscular injection	Every 2 - 3 wk	Short duration of action allows drug withdrawal if there are adverse side effects	Levels fluctuate

Do the Effects of Testosterone on Muscle Strength, Physical Function, Body Composition, And Quality of Life Persist Six Months after Treatment in Intermediate-Frail and Frail Elderly Men?



(A), LBM (B), AMS somatic symptoms (C), and (D) AMS sexual symptoms.

JCEM, February 2011, 96(2):454–458

British Society for Sexual Medicine recommendations for UK practice

Recommendations—screening

Screen for TD in adult men with **consistent and multiple signs of TD**

Screen all men presenting with **ED, loss of spontaneous erections, or low sexual desire**

Screen for TD in all men with **type 2 diabetes, BMI > 30 kg/m2, or waist circumference > 102 cm**

Screen for TD in all men on **long-term opiate, antipsychotic, or anticonvulsant medication**

Recommendations—diagnosis

Restrict diagnosis of TD to men with **persistent symptoms suggesting TD and confirmed low T level**

Measure **fasting T levels in the morning before 11 AM**, acknowledging that, in normal life, non-fasting levels could be up to 30% lower

Repeat **TT assessment on 2 occasions by a reliable method**; in addition, measure free T in men with levels close to **lower normal range (8-12 nmol/L)** or those with suspected or known abnormal SHBG level

Measure **LH serum levels to differentiate primary from secondary TD**

Base decisions on therapy on published action levels rather than laboratory reference ranges

Recommendations—initiating T therapy

- Perform cardiovascular, prostate, breast, and hematologic assessments before start of treatment
- Offer T therapy to symptomatic men with TD syndrome for treated localized low-risk prostate cancer (Gleason score < 8, stages 1-2, preoperative PSA level < 10 ng/mL, and not starting before 1 y of follow-up) and without evidence of active disease (based on measurable PSA level, DRE result, and evidence of metastatic disease)
- Assess cardiovascular risk factors before commencing T therapy and optimize secondary prevention in men with established disease

Recommendations—benefits and risks of T therapy

- Beyond 6 months. there is evidence of benefit for T therapy in **body composition, bone mineralization, and features of metabolic syndrome.**
- T therapy improves sexual desire, erectile function, and sexual satisfaction
- Decreases in BMI and waist size and improved glycemic control and lipid profile are observed in hypogonadal men receiving T therapy
- Trials of T therapy should be 6 months and maximal benefit is often seen beyond 12 months
- Fully inform the patient about expected benefits and side effects of therapy and facilitate a joint decision by an informed patient and physician
- Fully discuss the adverse effect of T therapy and its future reversibility on future fertility for each patient and his partner and offer alternative treatment as necessary
- In patients with adult-onset TD, when TRT is prescribed, offer weight-loss and lifestyle advice as standard management
- In **severely symptomatic patients with TT levels < 8 nmol/L lifestyle and dietary advice alone is unlikely to produce meaningful clinical improvement** within a relevant clinical period

Recommendations—follow-up

- Assess response to therapy at 3, 6, and 12 mo and every 12 mo thereafter
- Aim for a target TT level of **15 - 30 nmol/L** to achieve optimal response
- Monitor hematocrit before treatment, at 3 - 6 mo, 12 mo, and every 12 mo thereafter; decrease dosage, or switch preparation, if hematocrit is >0.54; if hematocrit remains high, consider stopping and reintroduce at a lower dose
- Assess prostate health by PSA and DRE before commencing TRT followed by PSA at 3 6 mo, 12 mo, and every 12 mo thereafter
- Assess cardiovascular risk before TRT is initiated and monitor cardiovascular risk factors throughout therapy

Summary

- TD is a well-established and significant medical condition, encompassing somatic, sexual, and psychological effects.
- It also is associated with increased CV and all-cause mortality.
- Clearly defined clinical symptoms should prompt swift evaluation of these and the underlying risk factors, and further investigations should be performed when appropriate.
- To identify individuals who should be screened for TD, consideration should be given to routinely asking men those at high risk. These include men with diabetes, osteoporosis or fragility fractures, CVD, ED, and depression and those on long-term opiate or oral glucocorticoid therapy.
- T therapy is based on evidence, effective, and safe, and treatment-related sustained normalization of serum T levels is probably associated with lower mortality.