Grazie dell'attenzione!

This Year in Gonads

Maurizio Merico, MD

Dipartimento Strutturale Aziendale Medicina
U.O.C. Andrologia e Medicina della Riproduzione
Ambulatorio di Endocrinologia, Andrologia ed Osteoporosi.
Policlinico Universitario - Padova

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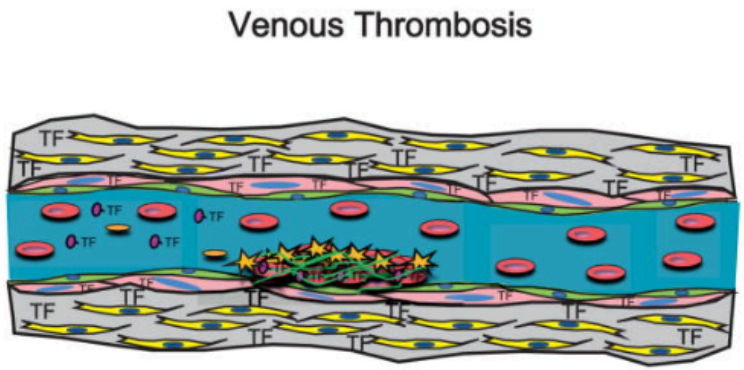
Segretario AME Veneto-Trentino Alto Adige

- Ai sensi dell'art. 3.3 sul conflitto di interessi, pag 17 del Regolamento Applicativo Stato-Regioni del 5/11/2009, dichiaro che negli ultimi 2 anni non ho avuto rapporti diretti di finanziamento con i soggetti portatori di interessi commerciali in campo sanitario.

Eventi trombo-embolici e testosterone

?



Published in final edited form as:
Thromb Haemost. 2010 September ; 104(3): 432–439. doi:10.1160/TH09-11-0771.

Tissue factor and thrombosis: The clot starts here

A. Phillip Owens III and **Nigel Mackman**

Eventi trombo-embolici e testosterone

CLINICAL PRACTICE GUIDELINE

Testosterone Therapy in Men With Hypogonadism: An Endocrine Society* Clinical Practice Guideline

Shalender Bhasin,[1] Juan P. Brito,[2] Glenn R. Cunningham,[3] Frances J. Hayes,[4] Howard N. Hodis,[5] Alvin M. Matsumoto,[6] Peter J. Snyder,[7] Ronald S. Swerdloff,[8] Frederick C. Wu,[9] and Maria A. Yialamas[10]

Case-control and pharmacoepidemiologic studies have not shown a consistent increase in the risk of venous thromboembolism (VTE) with T treatment.

However, there are too few T-associated VTE events in RCTs to draw meaningful inferences.

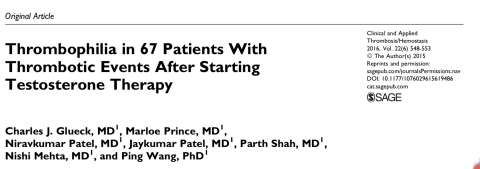
Some case reports have suggested that the risk for VTE may be increased in the presence of thrombophilia even without a raised hematocrit, especially within the first 6 months after starting T therapy.

The FDA has required manufacturers to include a warning about the risk of VTE for T products.

Eventi trombo-embolici e testosterone

Roma, 8-11 novembre 2018

ITALIAN CHAPTER


Original Article

Thrombophilia in 67 Patients With Thrombotic Events After Starting Testosterone Therapy

Charles J. Glueck, MD[1], Marloe Prince, MD[1], Niravkumar Patel, MD[1], Jaykumar Patel, MD[1], Parth Shah, MD[1], Nishi Mehta, MD[1], and Ping Wang, PhD[1]

Clinical and Applied Thrombosis/Hemostasis 2016, Vol. 22(6) 548-553 © The Author(s) 2015 Reprints and permission: sagepub.com/journalsPermissions.nav DOI: 10.1177/1076029615619486 cat.sagepub.com SAGE

TESTOSTERONE

- hypertension
- elevated hemoglobin
- low high-density lipoprotein cholesterol
- polycythemia
- hyperviscosity
- platelet aggregation

Familiar thrombophilia

Acquired thrombophilia

Eventi trombo-embolici nei pazienti in terapia con testosterone

Original Article

Thrombophilia in 67 Patients With Thrombotic Events After Starting Testosterone Therapy

Clinical and Applied Thrombosis/Hemostasis
2016, Vol. 22(6) 548-553
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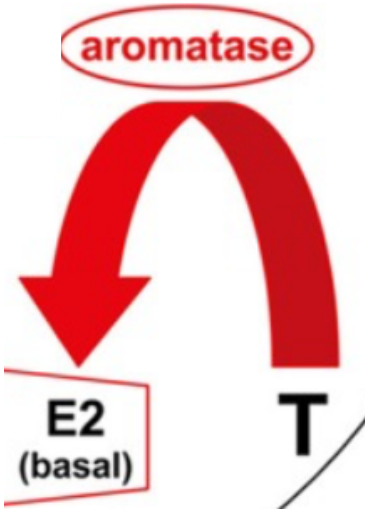
Charles J. Glueck, MD[1], Marloe Prince, MD[1], Niravkumar Patel, MD[1], Jaykumar Patel, MD[1], Parth Shah, MD[1], Nishi Mehta, MD[1], and Ping Wang, PhD[1]

Testosterone therapy also increases circulating estrogens that subsequently play a role in thrombotic events. Given that T is aromatized to estradiol (E2), it may be prothrombotic by the same mechanism as reported in women, where hormone replacement therapy interacts with the factor V Leiden mutation to increase the risk of venous thromboembolism.



Eventi trombo-embolici e testosterone: studio caso-controllo

Exposure to testosterone therapy in the 15 days before the event/index date was not associated with an increased risk of VTE

Mayo Clin Proc. 2015 Aug;90(8):1038-45. doi: 10.1016/j.mayocp.2015.05.012. Epub 2015 Jul 20.

Risk of Venous Thromboembolism in Men Receiving Testosterone Therapy.

Baillargeon J[1], Urban RJ[2], Morgentaler A[3], Glueck CJ[4], Baillargeon G[5], Sharma G[6], Kuo YF[7].

Author information

Abstract

OBJECTIVE:

To examine the risk of venous thromboembolism (VTE) associated with exposure to testosterone therapy in middle-aged and older men.

PATIENTS AND METHODS:

We conducted a case-control study of 30,572 men 40 years and older who were enrolled in one of the nation's largest commercial insurance programs between January 1, 2007, and December 31, 2012. Cases were defined as men who had a primary diagnosis of VTE and received an anticoagulant drug in the 60 days after their diagnoses. Cases were matched with 3 controls on event/index month, age, geographic region, diagnosis of hypogonadism, and diagnosis of any underlying prothrombotic condition. Conditional logistic regression analysis was used to calculate adjusted odds ratios (aORs) and 95% CIs for the risk of VTE associated with previous exposure to testosterone therapy.

RESULTS:

Exposure to testosterone therapy in the 15 days before the event/index date was not associated with an increased risk of VTE (aOR, 0.90; 95% CI, 0.73-1.12). None of the specific routes of administration examined were associated with an increased risk of VTE (topical [aOR, 0.80; 95% CI, 0.61-10.41], transdermal [aOR, 0.91; 95% CI, 0.38-2.16], and intramuscular [aOR, 1.15; 95% CI, 0.80-1.64]). These findings persisted using exposure windows that extended to 30 and 60 days before the event/index date.

CONCLUSION:

Having filled a prescription for testosterone therapy was not associated with an increased risk of VTE in commercially insured middle-aged and older men. These findings may provide clinically relevant information about the benefit-risk assessment for men with testosterone deficiency considering treatment.

Eventi trombo-embolici e testosterone: studio caso-controllo

RESEARCH

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Testosterone treatment and risk of venous thromboembolism: population based case-control study

Carlos Martinez,[1] Samy Suissa,[2] Stephan Rietbrock,[1] Anja Katholing,[1] Ben Freedman,[3,4,5] Alexander T Cohen,[6] David J Handelsman[3]

19 215 patients with confirmed venous thromboembolism (comprising deep venous thrombosis and pulmonary embolism) and 909 530 age matched controls from source population including more than 2.22 million men between January 2001 and May 2013.

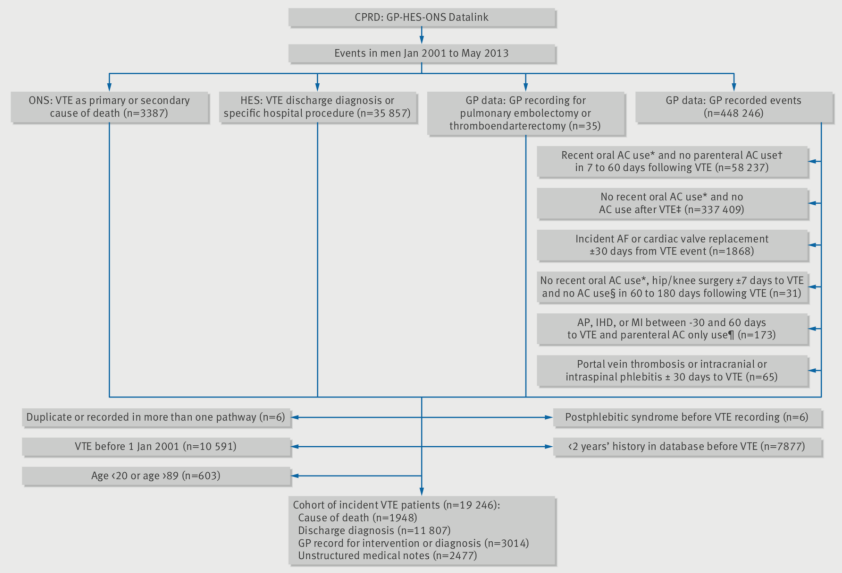


Fig 1 | Ascertainment of first venous thromboembolism (VTE) among 2.92 million men in CPRD-HES-ONS January 2001 to May 2013. AC=anticoagulant; AF=atrial fibrillation; AP=angina pectoris; CRPD=Clinical Practice Research Datalink; GP=general practitioner; HES=Hospital Episode Statistics; IHD=ischaemic heart disease; INR=international normalised ratio; LMWH=low molecular weight heparin; MI=myocardial infarction; ONS=Office for National Statistics. *Prescription for oral AC or ≥3 INR tests 31-180 days before VTE. †LMWH prescription. ‡Oral AC use or ≥3 INR tests within −7 to 60 days of VTE or ≥2 LMWH prescriptions within 7 to 60 days after VTE. §Oral AC prescription, LMWH prescription, or INR test. ¶LMWH prescription and no oral AC prescription within −30 to 60 days of VTE

Eventi trombo-embolici e testosterone: studio caso-controllo

Starting testosterone treatment was associated with an increased risk of venous thromboembolism, which peaked within six months and declined thereafter

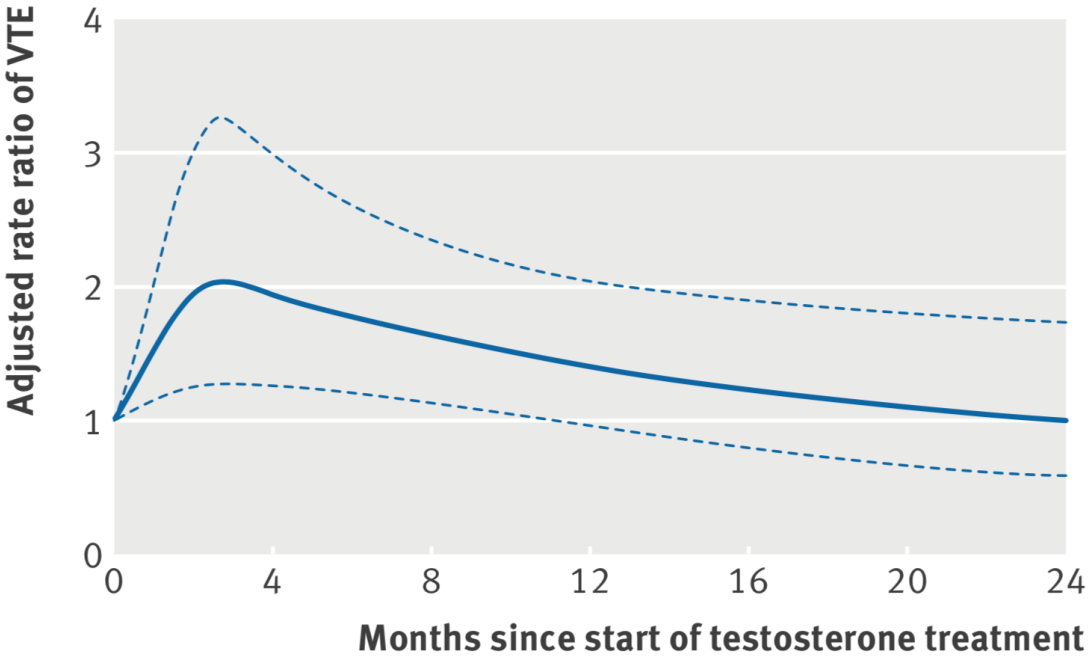
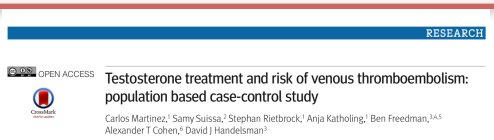


Fig 2 | Adjusted rate ratio of venous thromboembolism (VTE) and 95% confidence limits by time on current testosterone treatment. Testosterone treatment includes first time and repeat testosterone use

Eventi trombo-embolici e testosterone nell'ipogonadismo "non patologico"


RESEARCH

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Testosterone treatment and risk of venous thromboembolism: population based case-control study

Carlos Martinez,[1] Samy Suissa,[2] Stephan Rietbrock,[1] Anja Katholing,[1] Ben Freedman,[3,4,5] Alexander T Cohen,[6] David J Handelsman[7]

The risk of venous thromboembolism adjusted for underlying risk factors in association with testosterone use was increased early after the start of treatment for men without pathological hypogonadism, a group in which unproven empirical testosterone treatment has been increasingly used over the first decade of this century.

Table 2 | Crude and adjusted rate ratios of venous thromboembolism (VTE) stratified by history of pathological hypogonadism

	No (%)		Rate ratio (95% CI)	
	Cases	Controls	Crude	Adjusted*
Complete study cohort	(n=19 215)	(n=909 530)		
No testosterone treatment	19 124 (99.53)	907 433 (99.77)	1	1
Current testosterone treatment†	69 (0.36)	1251 (0.14)	1.84 (1.42 to 2.38)	1.25 (0.94 to 1.66)
Started ≤6 months before	36 (0.19)	529 (0.06)	2.26 (1.58 to 3.23)	1.63 (1.12 to 2.37)
Started >6 months before	33 (0.17)	722 (0.08)	1.53 (1.06 to 2.21)	1.00 (0.68 to 1.47)
Recent testosterone use‡	22 (0.11)	846 (0.09)	0.88 (0.57 to 1.36)	0.68 (0.43 to 1.07)
Without pathological hypogonadism	(n=18 475)	(n=890 127)		
No testosterone treatment	18 447 (99.85)	888 997 (99.87)	1	1
Current testosterone treatment†	21 (0.11)	530 (0.06)	1.91 (1.23 to 2.96)	1.69 (1.09 to 2.63)
Started ≤6 months before	11 (0.06)	252 (0.03)	2.06 (1.12 to 3.77)	1.88 (1.02 to 3.45)
Started >6 months before	10 (0.05)	278 (0.03)	1.77 (0.94 to 3.33)	1.53 (0.81 to 2.88)
Recent testosterone use‡	7 (0.04)	600 (0.07)	0.54 (0.26 to 1.15)	0.50 (0.24 to 1.05)
With pathological (primary or secondary) hypogonadism	(n=740)	(n=19 403)		
No testosterone treatment	677 (91.49)	18 436 (95.02)	1	1
Current testosterone treatment†	48 (6.49)	721 (3.72)	1.81 (1.31 to 2.50)	1.08 (0.75 to 1.55)
Started ≤6 months before	25 (3.38)	277 (1.43)	2.39 (1.53 to 3.75)	1.52 (0.94 to 2.46)
Started >6 months before	23 (3.11)	444 (2.29)	1.44 (0.92 to 2.26)	0.82 (0.50 to 1.32)
Recent testosterone use‡	15 (2.03)	246 (1.27)	1.30 (0.74 to 2.28)	0.84 (0.46 to 1.52)

*Adjusted for age, history of primary or secondary hypogonadism, surgical procedures, medical illness, trauma, and active cancer in 90 days before index date and for history of cancer ≥91 days before index date (matching factors); for smoking, body mass index, alcohol, socioeconomic status, any history of polycythaemia, chronic pulmonary disease, diabetes, congestive heart failure, myocardial infarction, peripheral vascular disease and stroke, sexual dysfunction, tiredness, and covariate comprising osteoporosis, infertility, loss of appetite, and hot flushes; and for use of corticosteroids, megestrol, non-steroidal anti-inflammatory drugs, and antiplatelets within 90 days of index date.
†Defined as prescription for which duration included index date.
‡Defined as use that ended between two years and one day before index date.

Eventi trombo-embolici e testosterone: solo nei primi 3 mesi, poi fibrinolisi

transient increased risk due to testosterone treatment

effects on thrombosis via decreased fibrinolysis

previously undiagnosed thrombophilia-hypofibrinolysis

higher underlying cardiovascular risk associated with erectile dysfunction

RESEARCH

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Testosterone treatment and risk of venous thromboembolism: population based case-control study

Carlos Martinez,[1] Samy Suissa,[2] Stephan Rietbrock,[1] Anja Katholing,[1] Ben Freedman,[3,4,5] Alexander T Cohen,[6] David J Handelsman[3]

Eventi trombo-embolici e testosterone: solo nei primi 3 mesi, poi fibrinolisi

The initial increased risk of venous clotting might provoke a secondary response with more fibrinolysis, which tends to dissolve clots and eventually neutralises the risk.

Table 3 | Crude and adjusted rate ratios of venous thromboembolism (VTE) stratified by route of administration of testosterone treatment and VTE risk factor status

	No (%)		Rate ratio (95% CI)	
	Cases	Controls	Crude	Adjusted*
Route of administration	(n=19 215)	(n=909 530)		
No recent testosterone treatment	19 124 (99.53)	907 433 (99.77)	1	1
Current testosterone treatment†				
Intramuscular	40 (0.21)	678 (0.07)	1.88 (1.34 to 2.64)	1.24 (0.87 to 1.77)
Transdermal	24 (0.12)	453 (0.05)	1.87 (1.21 to 2.87)	1.31 (0.84 to 2.04)
Oral	5 (0.03)	97 (0.01)	1.76 (0.69 to 4.53)	1.32 (0.49 to 3.55)
Implant	0	23	–	–
Without known VTE risk factors	(n=9770)	(n=488 461)		
No testosterone treatment	9726 (99.55)	487 270 (99.76)	1	1
Current testosterone treatment†	37 (0.38)	784 (0.16)	2.46 (1.75 to 3.46)	1.57 (1.06 to 2.32)
Started ≤6 months before	17 (0.17)	321 (0.07)	2.75 (1.68 to 4.50)	1.91 (1.13 to 3.23)
Started >6 months before	20 (0.20)	463 (0.09)	2.25 (1.43 to 3.56)	1.35 (0.82 to 2.24)
Recent testosterone use§	7 (0.07)	407 (0.08)	0.88 (0.42 to 1.86)	0.62 (0.29 to 1.33)
With known VTE risk factors	(n=9445)	(n=421 069)		
No testosterone treatment	9398 (99.50)	420 163 (99.78)	1	1
Current testosterone treatment†	32 (0.34)	467 (0.11)	1.36 (0.92 to 2.00)	0.99 (0.65 to 1.49)
Started ≤6 months before	19 (0.20)	208 (0.05)	1.89 (1.13 to 3.15)	1.41 (0.82 to 2.41)
Started >6 months before	13 (0.14)	259 (0.06)	0.96 (0.53 to 1.73)	0.68 (0.37 to 1.27)
Recent testosterone use§	15 (0.16)	439 (0.10)	0.87 (0.51 to 1.49)	0.70 (0.39 to 1.23)

*Adjusted for age, history of primary or secondary hypogonadism, surgical procedures, medical illness, trauma, and active cancer in 90 days before index date and for history of cancer ≥91 days before index date (matching factors); for smoking, body mass index, alcohol, socioeconomic status, any history of polycythaemia, chronic pulmonary disease, diabetes, congestive heart failure, myocardial infarction, peripheral vascular disease and stroke, sexual dysfunction, tiredness, and covariate comprising osteoporosis, infertility, loss of appetite, and hot flushes; and for use of corticosteroids, megestrol, non-steroidal anti-inflammatory drugs, and antiplatelets within 90 days of index date.
†Defined as prescription for which duration included index date.
‡Defined as hospital diagnosis of medical condition or trauma or in-hospital surgical procedure in 90 days before index VTE, or history of cancer recorded any time before index date.
§Defined as use that ended between two years and one day before index date.

RESEARCH

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Testosterone treatment and risk of venous thromboembolism: population based case-control study

Carlos Martinez,[1] Samy Suissa,[2] Stephan Rietbrock,[1] Anja Katholing,[1] Ben Freedman,[3,4,5] Alexander T Cohen,[6] David J Handelsman[3]

Effetti trombo-embolici e testosterone? Studi sperimentali nella deprivazione a.

Independent of any other risk factors, testosterone deficiency induces platelets aggregation and hypercoagulation and inhibits fibrinolysis, effects that can be reversed by testosterone therapy

Platelets, 2018 Aug 13:1-7. doi: 10.1080/09537104.2018.1499886. [Epub ahead of print]

Administration of testosterone improves the prothrombotic and antifibrinolytic parameters associated with its deficiency in an orchidectiomized rat model.

Alqahtani SA1, Alhawiti NM2.

Abstract

This study investigated the effect of testosterone deficiency and replacement on platelets function and aggregation, coagulation, and fibrinolysis in young adult healthy male rats. Rats were classified into three groups (n = 6/group) of either "a sham-operated+ vehicle," "an orchidectomized (ORX)+ vehicle," and "an ORX+testosterone propionate (0.5 mg/kg, 3X/week, S.C)." All treatments were carried out for 12 weeks. Our results showed that ORX rats had induced platelets aggregation and coagulation and inhibited fibrinolysis. ORX-induced rats had increased ratios of adenosine diphosphate-induced aggregation, shorter bleeding time, clotting time, prothrombin time, and activated partial thromboplastin time and their sera showed increased levels of thromboxane B2 and fibrinogen levels. Concomitantly, their plasma showed increased TPA-1 and decreased tissue plasminogen activator (tPA) levels. At molecular levels, the aorta of ORX-induced rats showed increased aortic mRNA and protein levels of plasminogen activator inhibitor-1 (PAI-1), protein levels of von Willebrand Factor (vWF) and decreased mRNA and protein levels of tPA, and their liver showed increased protein levels of prothrombin and factor VII. Testosterone post-therapy to ORX-induced rats significantly reversed all these hematological and molecular changes. In conclusion, independent of any other risk factors, testosterone deficiency induces platelets aggregation and hypercoagulation and inhibits fibrinolysis, effects that can be reversed by testosterone therapy.

Eventi trombo-embolici nella deprivazione androgenica

Urology. 2018 Apr;114:155-162. doi: 10.1016/j.urology.2017.11.055. Epub 2018 Jan 17.

Association of Androgen Deprivation Therapy and Thromboembolic Events: A Systematic Review and Meta-analysis.

Nead KT1, Boldbaatar N2, Yang DD2, Sinha S2, Nguyen PL2.

OBJECTIVES:
To investigate the association of androgen deprivation therapy (ADT) for prostate cancer with thromboembolic events.

METHODS:
PubMed, Web of Science, and Scopus were queried on April 5, 2017 for systematic review. Additionally, The World Health Organization International Trials Registry Platform was queried on June 23, 2017. Eligible studies reported thromboembolic events among individuals with prostate cancer exposed to ADT vs a lesser-exposed group. Five hundred sixty-nine unique studies were identified with 65 undergoing full-text review. We utilized the Meta-analysis of Observational Studies in Epidemiology statement guidelines and the Cochrane Review Group's data extraction template. Study quality was evaluated by Newcastle-Ottawa Scale criteria. We conducted random-effects meta-analyses to calculate summary statistic risk ratios and 95% confidence intervals. Heterogeneity was quantified using the I^2 statistic. Small study effects were evaluated using Begg and Egger statistics.

RESULTS:
In 10 studies "ADT without estrogen" increased the risk of thromboembolic events (risk ratio [RR] 1.43, 95% confidence interval [CI] 1.15-1.77, P = .001). In 9 studies estrogen therapy alone was associated with an increased risk of thromboembolic events (RR 3.72, 95% CI 1.78-7.80, P <.001). We found an increased risk of thromboembolic events from ADT use without estrogen when limited to localized disease (RR 1.10, 95% CI 1.05-1.16, P <.001). Heterogeneity was resolved in those studies examining localized disease. There was no evidence of small study effects.

CONCLUSION:
The currently available evidence suggests that ADT without estrogen is associated with an increased the risk of thromboembolic events.

Eventi trombo-embolici nella deprivazione androgenica

Prostate Cancer Prostatic Dis. 2018 Jul 9. doi: 10.1038/s41391-018-0059-4. [Epub ahead of print]

Association of androgen deprivation therapy with thromboembolic events in patients with prostate cancer: a systematic review and meta-analysis.

Guo Z1, Huang Y1, Gong L2, Gan S3, Chan FL4, Gu C3, Xiang S3, Wang S5.

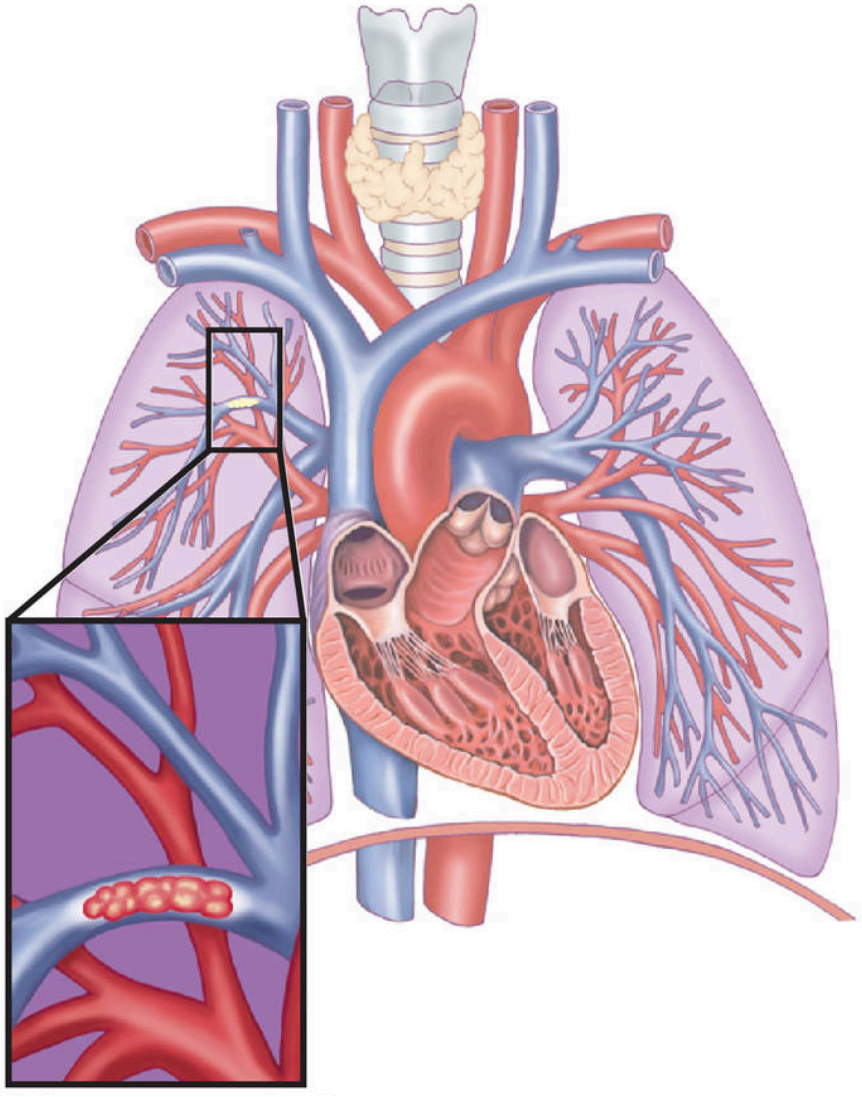
BACKGROUND:
Whether androgen deprivation therapy (ADT) causes excess thromboembolic events (TEs) in men with prostate cancer (PCa) remains controversial and is the subject of the US Food and Drug Administration safety warning. This study aims to perform a systematic review and meta-analysis on previous studies to determine whether ADT is associated with TEs in men with PCa.

METHODS:
Medline, Embase, and Cochrane Library databases were searched for relevant studies. These studies comprised those that compared ADT versus control to treat PCa, reported TEs as outcome, and were published before January 2018. Multivariate adjusted hazard ratios (HRs) and associated 95% confidence intervals (CIs) were calculated using random- or fixed-effects models.

RESULTS:
Five retrospective population-based cohort studies involving 170,851 ADT users and 256,704 non-ADT users were identified. Deep venous thrombosis (DVT) was found significantly associated with gonadotropin-releasing hormone (GnRH) agonists alone (HR = 1.47, 95% CI: 1.07-2.03; P = 0.017; I^2 = 96.3%), GnRH agonists plus oral antiandrogen (AA) (HR = 2.55, 95% CI: 2.21-2.94; P < 0.001; I^2 = 0.0%), and AA alone (HR = 1.49, 95% CI: 1.13-1.96; P = 0.004; I^2 = 0.0%), but not with orchiectomy (HR = 1.80, 95% CI: 0.93-3.47; P = 0.079; I^2 = 94.8%). In addition, pulmonary embolism (PE) was significantly associated with GnRH agonists alone (HR = 2.26, 95% CI: 1.78-2.86; P < 0.001; I^2 was unavailable) and orchiectomy (HR = 2.12, 95% CI: 1.44-3.11; P < 0.001; I^2 = 57.2%). This relationship was also supported with subgroup analyses based on different continents and races.

CONCLUSIONS:
GnRH agonists alone, GnRH plus AA, and AA alone cause excess DVT in men with PCa after controlling the demographic and disease characteristics and other confounding factors, although statistically significant difference was not observed in orchiectomy group. Additionally, GnRH agonists alone and orchiectomy can increase the incidence of PE.

Eventi trombo-embolici e testosterone: effetti dell'olio sull'embolismo polmonare




RESEARCH

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Testosterone treatment and risk of venous thromboembolism: population based case-control study

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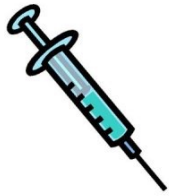

Furthermore, venous thromboembolism should not be confused with pulmonary oil microembolisation, an immediate and transient effect of depot injections of testosterone esters in an oil vehicle

Eventi trombo-embolici nei pazienti in terapia con testosterone

Comparison of thrombophilia in 67 cases (59 men and 8 women) with thrombotic events after starting testosterone therapy (TT) versus 111 patient controls having unprovoked venous thrombotic events without TT

Original Article

Thrombophilia in 67 Patients With Thrombotic Events After Starting Testosterone Therapy

Clinical and Applied Thrombosis/Hemostasis 2016, Vol. 22(6) 548-553 © The Author(s) 2015 Reprints and permission: sagepub.com/journalsPermissions.nav DOI: 10.1177/1076029615619486 cat.sagepub.com SAGE

Charles J. Glueck, MD[1], Marloe Prince, MD[1], Niravkumar Patel, MD[1], Jaykumar Patel, MD[1], Parth Shah, MD[1], Nishi Mehta, MD[1], and Ping Wang, PhD[1]

Table 1. Demographics of 67 Patients With Thrombotic Events After Starting TT and 111 Controls With Thrombotic Events Not Receiving TT.

Cases: 67 Patients With Thrombotic Events After Starting TT				Controls: Thrombotic Events Without TT
Gender	Male: 59 (88%), female: 8 (12%)			Male: 53 (48%), F: 58 (52%), $P < .0001$ (Fisher)
Age, years	52 ± 14, median: 53, 25th-75th percentile: 43-62, range: 21-82			57 ± 15, median: 60, range: 16-94, $P = .04$ (Wilcoxon)
Time from T treatment to thrombotic events, months	10.7 ± 13.3, median: 6, 25th-75th percentile: 3-12, range: 0.2-72			
TT	TT	n (%)	Dose (Mean ± SD, Median, Range)	
	Gel	39 (58%)	59 ± 30, 50, 20-160 mg/d	
	Intramuscular	21 (31%)	160 ± 97, 200, 50-400 mg/wk	
	HCG	2 (3%), 1 also had gel	3000 IU/wk	
	Patch	2 (3%)	4 mg/d	
	Pellet	3 (4%)	75 mg every 3 months	
	Clomid	1 (1%)	25 mg/d	
Thrombotic events[a]	Event Type	n (%)		n (%)
	DVT-PE	47 (70%)		75 (68%)
	Osteonecrosis	16 (24%)		23 (21%)
	Ocular thrombosis (1 also had osteonecrosis)	4 (6%)		13 (12%)

Abbreviations: DVT, deep venous thrombosis; HCG, human chorionic gonadotropin; PE, pulmonary embolism; SD, standard deviation; TT, testosterone therapy.
[a] The thrombotic event types did not differ between cases and controls, Fisher's $P = .47$.

Eventi trombo-embolici nei pazienti in terapia con testosterone

Original Article

Clinical and Applied Thrombosis/Hemostasis 2016, Vol. 22(6) 548-553

DOI: 10.1177/1076029615619486
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Thrombophilia in 67 Patients With Thrombotic Events After Starting Testosterone Therapy

Charles J. Glueck, MD[1], Marloe Prince, MD[1], Niravkumar Patel, MD[1], Jaykumar Patel, MD[1], Parth Shah, MD[1], Nishi Mehta, MD[1], and Ping Wang, PhD[1]

Cases differed from controls for factor V Leiden heterozygosity (16 of the 67 [24%] vs 13 [12%] of the 111, P = .038) and for lupus anticoagulant (9 [14%] of the 64 vs 4 [4%] of the 106, P = .019). After a first thrombotic event and continuing TT, 11 cases had a second thrombotic event, despite adequate anticoagulation, 6 of whom, still anticoagulated, had a third thrombosis.

Table 2. Thrombophilia in 67 Patients With DVT-PE 6 Months (Median) After Starting TT (TT-VTE) Compared to 111 Controls With DVT-PE Not Taking TT (VTE-No TT).

	Factor V	PTG	Factor VIII	Factor XI	Homocysteine[a]	Lupus anticoagulant	Protein C	Protein S	Free S	MTHFR	PAIG	Antithrombin III	ACLA IgG	ACLA IgM
Normal range	CC	CC	≤150%	≤150%	Umol/L	Negative	≥73	≥63	≥66	CC	5G5G	≥80	Dated[b]	Dated[c]
Cases: TT-VTE	16/67 (24%)	5/66 (8%)	18/63 (29%)	6/63 (10%)	12/66 (18%)	9/64 (14%)	11/50 (22%)	6/47 (13%)	8/38 (21%)	14/46 (30%)	17/47 (36%)	4/46 (9%)	2/51 (4%)	5/52 (10%)
Controls: VTE-no TT	13/111 (12%)	7/109 (6%)	39/107 (36%)	22/109 (20%)	24/106 (23%)	4/106 (4%)	21/106 (20%)	12/105 (11%)	24/86 (28%)	31/101 (31%)	34/101 (34%)	3/103 (3%)	4/109 (4%)	14/109 (13%)
Fisher *P*	**.038**	.77	.32	.087	.57	**.019**	.83	.79	.51	1	.85	.2	1	.61

Values in bold are statistically significant. Abbreviations: ACLA, anticardiolipin antibody; CC, wild-type normal; DVT, deep venous thrombosis; Ig, immunoglobulin; PAIG, plasminogen activator inhibitor gene; PE, pulmonary embolism; PTG, prothrombin gene mutation; TT, testosterone therapy; VTE, venous thromboembolism. [a] Dated cut point for homocysteine high: ≥13.5 Umol/L (before March 20, 2005); ≥12 (March 21, 2005, to March 27, 2006); ≥10.4 (March 28, 2006, to April 14, 2008); ≥11.4 (April 15, 2008, November 14, 2008); ≥15 (November 15, 2008, to December 02, 2014); ≥10.4 (after December 03, 2014). [b] Dated cut point for IgG high: ≥23 GPL (before October 31, 2012); ≥15 (after November 01, 2012). [c] Dated cut point for IgM high: ≥10 MPL (before April 30, 2012); ≥13 (after May 01, 2012).

Eventi trombo-embolici nei pazienti in terapia con testosterone

Original Article

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Thrombophilia in 67 Patients With Thrombotic Events After Starting Testosterone Therapy

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Screening for thrombophilia before starting TT should identify men and women at high risk for thrombotic events with an adverse risk–benefit ratio for TT.

When TT is given to patients with familial and acquired thrombophilia, thrombosis may occur and recur in thrombophilic men despite anticoagulation.

Eventi trombo-embolici e testosterone: gruppo particolare (Klinefelter)

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Original Article

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Thrombophilia in Klinefelter Syndrome With Deep Venous Thrombosis, Pulmonary Embolism, and Mesenteric Artery Thrombosis on Testosterone Therapy: A Pilot Study

Charles J. Glueck, MD[1,2], Vybhav Jetty, MD[1,2], Naila Goldenberg, MD[1,2], Parth Shah[1,2], and Ping Wang, PhD[2]

6 men with Klinefelter syndrome (KS), without previously known familial thrombophilia, who had sustained deep venous thrombosis (DVT)–pulmonary embolism (PE) or mesenteric artery thrombosis on testosterone replacement therapy (TRT)

Table 1. Current Age, Age at Diagnosis, TRT Dose, Time Interval Between Starting TRT and Development of DVT-PE, and Serum Total and Free Testosterone and Estradiol Levels on TRT.

ID	Current Age	Age at Diagnosis		TRT Dose	DVT-PE Developed (years) After TRT Started	Levels on TRT		
		KS	VTE			T 348-1197[a] (ng/dL)	Free T 6.6-18.1[a] (pg/mL)	Estradiol 7.8-42.6[a] (pg/mL)
1	22	11	22	Gel 50 mg/d	11 DVT-PE	668	11.5	26.7
2	52	48	49	Gel 50 mg/d	1 mesenteric artery thrombosis	903	18.8	32.0
			52	Clomid 75 mg/d	4 DVT-PE			
3	27	13	24	IM 300 mg every 2 weeks	11 DVT-PE	428	9.5	17.7
4	21	19	19.5	IM 40 mg twice/week	0.5 DVT-PE	660	1.8	—
5	72	12	61	Gel 50 mg/day	49 DVT-PE	8[b]	1.8[b]	4.0[b]
6	38	13	25	Gel 50 mg/d	12 DVT-PE	516	11.1	—

Abbreviations: DVT-PE, deep venous thrombosis–pulmonary emboli; KS, Klinefelter syndrome; TRT, testosterone replacement therapy; VTE, venous thromboembolism.
[a]Laboratory normal range.
[b]Not on TRT.

Eventi trombo-embolici e testosterone: gruppo particolare (Klinefelter)

Of the 6 men, 4 had high (>150%) factor VIII (177%, 192%, 263%, and 293%), 3 had high (>150%) factor XI (165%, 181%, and 193%), 1 was heterozygous for the factor V Leiden mutation, and 1 was heterozygous for the G20210A prothrombin gene mutation.

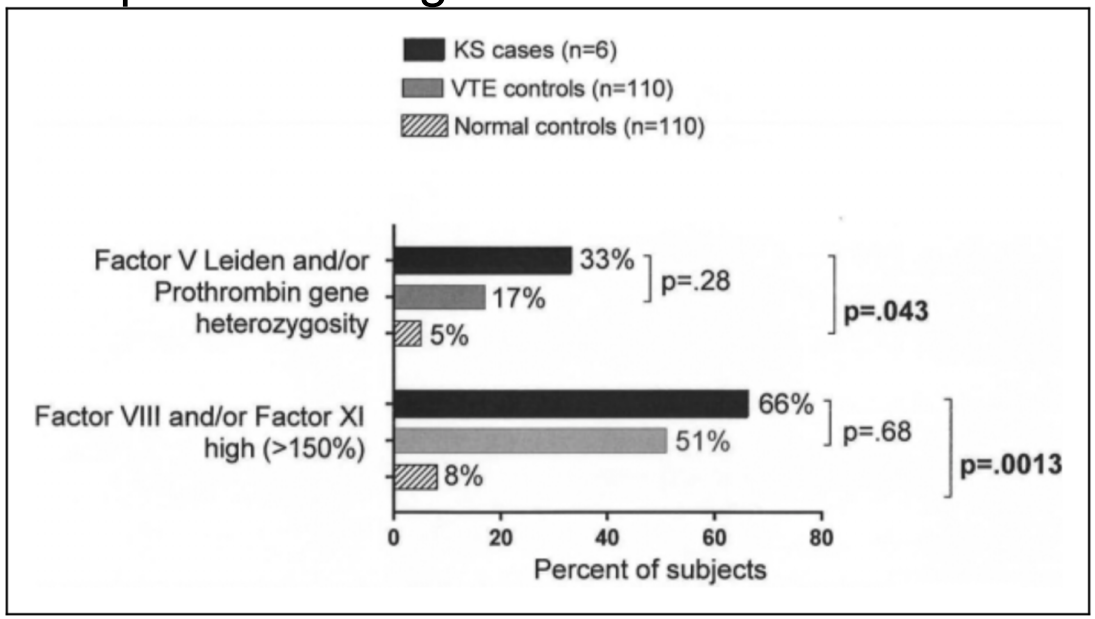

Figure 1. Factor V Leiden and/or G20210A PTG heterozygosity, elevated factor VIII and/or factor XI, in 6 patients with Klinefelter syndrome in 110 controls with VTE without concurrent TRT and in 110 healthy normal controls without TRT. PTG indicates prothrombin gene; TRT, testosterone replacement therapy; VTE, venous thromboembolism.


Original Article

Thrombophilia in Klinefelter Syndrome With Deep Venous Thrombosis, Pulmonary Embolism, and Mesenteric Artery Thrombosis on Testosterone Therapy: A Pilot Study

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None of the 6 men had a precipitating event before their deep venous thrombosis-pulmonary emboli.

Eventi trombo-embolici e testosterone: gruppo particolare (Klinefelter)

Original Article

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Table 2. Coagulation Measures in 6 Patients With Klinefelter Syndrome.

	Factor V Leiden	Prothrombin Gene mutation (PTG)	MTHFR	Plasminogen activator inhibitor gene (PAIG)	Homocysteine	Factor VIII	Factor XI	Protein C	Protein S	Free S	Antithrombin III	Lupus Anticoagulant
Abnormal range	**AA, AG**	**AA, AG**	**TT**	**4G4G**	**Dated cut point[a]**	**>150%**	**>150%**	**<73%**	**<63%**	**<66%**	**<80**	**Positive**
1	CC	CC	CC	5G5G	**15.6**	64	112	103	91	108	135	Negative
2	CC	CC	**TT**	—	11.4	**263**	**193**	137	113	—	105	Negative
3	CC	CC	CT	5G5G	11.3	**192**	104	**69**	90	90	104	Negative
4	CC	**AG**	CC	5G5G	8.0	110	126	92	—	**57**	83	Negative
5	**AG**	CC	CC	**4G4G**	13.4	**177**	**165**	105	100	72	108	Negative
6	CC	CC	**TT**	5G5G	—	**293**	**181**	—	—	—	—	Negative

[a]Dated cut point for homocysteine high: ≥13.5 µmol/L (before March 20, 2005); ≥12 µmol/L (March 21, 2005, to March 27, 2006); ≥10.4 µmol/L (March 28, 2006, to April 14, 2008); ≥11.4 µmol/L (April 15, 2008, to November 14, 2008); ≥15 (November 15, 2008, to December 2, 2014); ≥10.4 µmol/L (after December 3, 2014).

Values in bold indicate presence of thrombophilia.

Eventi trombo-embolici e testosterone: gruppo particolare (Klinefelter)

Original Article

Thrombophilia in Klinefelter Syndrome With Deep Venous Thrombosis, Pulmonary Embolism, and Mesenteric Artery Thrombosis on Testosterone Therapy: A Pilot Study

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Charles J. Glueck, MD[1,2], Vybhav Jetty, MD[1,2], Naila Goldenberg, MD[1,2], Parth Shah[1,2], and Ping Wang, PhD[2]

Table 3. Coagulation Disorders in 6 Patients With KS, Compared With 110 VTE Controls, and With 110 Healthy Normal Controls.

	Factor V Leiden	Prothrombin Gene mutation (PTG)	MTHFR	Plasminogen activator inhibitor gene (PAIG)	Factor VIII	Factor XI	Homocysteine[a]	Protein C	Protein S	Free S	Antithrombin III	Lupus Anticoagulant
Abnormal range	**AA, AG**	**AA, AG**	**TT**	**4G4G**	**>150%**	**>150%**	**Umol/L**	**<73%**	**<63%**	**<66%**	**<80**	**Positive**
KS cases (n = 6)	1/6 (17%)	1/6 (17%)	2/6 (33%)	1/5 (20%)	4/6 (67%)	3/6 (50%)	1/5 (20%)	1/5 (20%)	0/4 (0%)	1/4 (25%)	0/5 (0%)	0/6 (0%)
Compare to VTE controls (n = 110)	13/110 (12%)	7/108 (6%)	30/100 (30%)	33/100 (33%)	39/106 (37%)	22/108 (20%)	24/105 (23%)	21/105 (20%)	12/104 (12%)	24/85 (28%)	3/102 (3%)	4/105 (4%)
Fisher, *P*	.55	.36	1.0	1.0	.20	.12	1.0	1.0	1.0	1.0	1.0	1.0
Compare to healthy normal controls (n = 110)	2/109 (2%)	3/110 (3%)	32/109 (29%)	26/104 (25%)	7/103 (7%)	3/101 (3%)	5/107 (5%)	6/96 (6%)	4/96 (4%)	2/96 (2%)	2/96 (2%)	2/110 (2%)
Fisher, *P*	.15	.19	1.0	1.0	**.0008**	**.0019**	.24	.31	1.0	.12	1.0	1.0

Abbreviations: KS, Klinefelter syndrome; VTE, venous thromboembolism.
[a]Dated cut point for homocysteine high: ≥13.5 μmol/L (before March 20, 2005); ≥12 μmol/L (March 21, 2005, to March 27, 2006); ≥10.4 μmol/L (March 28, 2006, to April 14, 2008); ≥11.4 μmol/L (April 15, 2008, to November 14, 2008); ≥15 μmol/L (November 15, 2008, to December 2, 2014); ≥10.4 μmol/L (after December 3, 2014).

Eventi trombo-embolici e testosterone: metanalisi

Review

Testosterone treatment and cardiovascular and venous thromboembolism risk: what is 'new'?

G Corona,[1] M Dicuio,[2,3] G Rastrelli,[4] E Maseroli,[4] F Lotti,[4] A Sforza,[1] M Maggi[4]

The contribution of T as a risk factor for VTE in men is controversial.

Two large population-based studies failed to find an association between endogenous T and VTE.

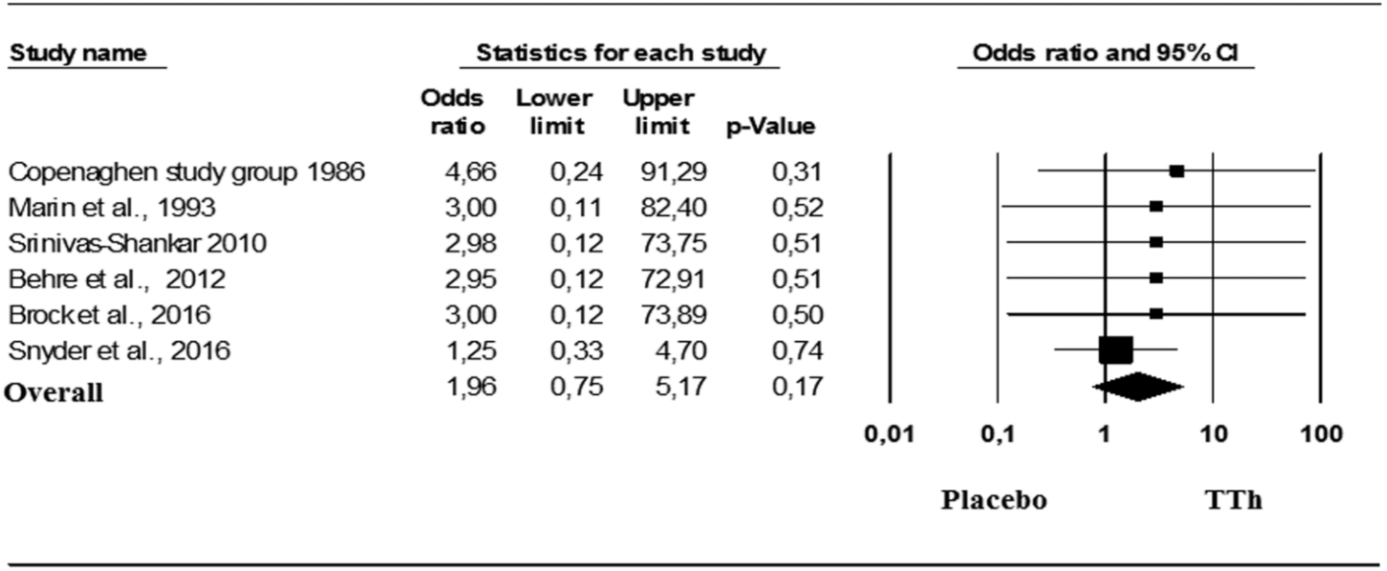

Figure 2 Forest plot of estimated OR (95% CIs) for venous thromboembolism (VTE) of testosterone treatment (TTh) versus placebo, as derived from available placebo-controlled available trials.

Eventi trombo-embolici e testosterone endogeno: non correlazione


Review

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G Corona,[1] M Dicuio,[2,3] G Rastrelli,[4] E Maseroli,[4] F Lotti,[4] A Sforza,[1] M Maggi[4]

Data from the fourth survey of the Tromsø study (1994–1995) — which included 1350 community-dwelling men aged 50–84 years — showed a lack of association between endogenous total and free T and risk of VTE.

Similar results were reported by Holmegard et al in the Copenhagen City Heart Study, including 4673 men representative for the adult Danish population. In line with these data, Mumoli et al were unable to detect any difference in T and oestradiol levels between 63 patients with unprovoked deep venous thrombosis (DVT) and matched controls.

Table 3 Characteristics of the longitudinal studies evaluating difference in testosterone (T) levels between subjects with or without venous thromboembolism (VTE) (upper panels) and risk for VTE as derived from available pharmacoepidemiological studies (lower panels)

Study (ref.)	No. of patients	Follow-up duration (years)	Age (years)	Body mass index	DM	Smoking	Unadjusted risk of VTE	Adjusted risk of VTE
Risk of VTE based on baseline T levels								
Svartberg *et al*,[51] 2009	1350	8	63±7	26.1±3.5	3.8	32.1	–	1.21 (0.62;2.44)*
Holmegard *et al*,[52] 2014	4673	21	57 (48–65)	26 (23–28)	13	64	–	1.30 (0.62;2.73)*
Mumoli *et al*,[53] 2015	126	2	64.6±14.2	26.7±2.8	–	–	–	No difference
Risk of VTE based on TTh exposition in case–control studies								
Baillargeon *et al*,[54] 2015	Cases 7643 Controls 22 929	–	≥ 40	–	–	–	0.92 (0.75;1.13)†	0.90 (0.73;1.12)†
Martinez *et al*,[55] 2016	Cases 19 215 Controls 909 530	–	64.8±15.2	26.0±4.6	–	19.8	1.84 (1.42;2.38)†	1.25 (0.94;1.66)†

*Highest versus lowest T quartile.
†Exposed versus unexposed to testosterone treatment (TTh).
DM, diabetes mellitus.

Eventi trombo-embolici e testosterone esogeno: no correlazione

Review

Testosterone treatment and cardiovascular and venous thromboembolism risk: what is 'new'?

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Table 4 Characteristics of the randomized, placebo-controlled clinical studies included in the meta-analysis on venous thromboembolism risk

Study (ref.)	No. of patients (T/placebo)	Trial duration (weeks)	Age (years)	Comorbidities	Baseline total T (nmol/L)	T levels	Dose
Copenhagen Study Group,[59] 1986	134/87	112	53.0	Alcoholic cirrhosis	NR	Mixed	Micronized T 600 mg/day
Marin *et al*,[60] 1993	11/10	32	57.2	Overweight/ obese	14.8	Mixed	TG 100 mg/day
Srinivas-Shankar *et al*,[61] 2010	136/138	26	73.8	Elderly frail men	11	Mixed	TG 50 mg/day
Behre *et al*,[62] 2012	183/179	48	62.0	Elderly men	10,5	Mixed	TG 50–75 mg/day
Brock *et al*,[63] 2016	358/357	12	55.3	Elderly men	6,9	<12 nM	T solution 2% 30–60 mg/day
Snyder *et al*,[64] 2016	395/395	52	72.2	Elderly men	8.2	<12 nM	TG 50–100 mg/day

T, testosterone; TG, testosterone gel.

Eventi trombo-embolici e testosterone: aumento eritrocitosi

J Clin Endocrinol Metab. 2018 Mar 17. doi: 10.1210/jc.2018-00404. [Epub ahead of print]

The efficacy and adverse events of testosterone replacement therapy in hypogonadal men: A systematic review and meta-analysis of randomized, placebo-controlled trials.

Ponce OJ[1,2,3], Spencer-Bonilla G[3,4], Alvarez-Villalobos N[3,5], Serrano V[3,6], Singh-Ospina N[7], Rodriguez-Gutierrez R[3,5], Salcido-Montenegro A[5], Benkhadra R[1], Prokop LJ[1,8], Bhasin S[9], Brito JP[3].

CONTEXT:

The efficacy and safety of testosterone replacement therapy (TRT) in hypogonadal men remain incompletely understood.

OBJECTIVE:

To conduct a systematic review and meta-analysis of randomized clinical trials (RCT) to determine the effects of TRT on patient-important outcomes and adverse events in hypogonadal men.

We searched Ovid MEDLINE, Ovid EMBASE, Ovid Cochrane Database of Systematic Reviews, Ovid Cochrane Central Register of Controlled Trials, and Scopus from inception to March 2th, 2017.

RCTs that assessed the efficacy and adverse events of TRT of at least 12 weeks compared with placebo in adult men with hypogonadism, defined by morning testosterone ≤300 ng/dL and at least one symptom or sign of hypogonadism.

Reviewers working independently and in duplicate assessed the quality of the trials and collected data on patient characteristics, interventions, and outcomes.

DATA SYNTHESIS:

We found 11 publications, reporting on 4 eligible trials (including 1,779 patients) at low risk of bias. Compared to placebo, TRT was associated with a small but significant increase in sexual desire or libido [standardized mean difference (SMD): 0.17, 95% CI 0.01, 0.34] (n=1383), erectile function [SMD: 0.16, 95% CI 0.06, 0.27] (n=1344), and sexual satisfaction [SMD: 0.16, 95% CI 0.01, 0.31] (n=676), but had no effect on energy or mood. TRT was associated with an increased risk of developing erythrocytosis [relative risk: 8.14, 95% CI: 1.87, 35.40] (n=1579) compared to placebo, but had no significant effect on lower urinary tract symptoms (LUTS).

CONCLUSION:

In hypogonadal men TRT improves sexual desire, erectile function, and sexual satisfaction, however it increases the risk of erythrocytosis.

Thromb Haemost. 2018 Oct 8. doi: 10.1055/s-0038-1673613. [Epub ahead of print]

Prospective Study of Endogenous Hormones and Incidence of Venous Thromboembolism: The Atherosclerosis Risk in Communities Study.

Roetker NS[1,2], MacLehose RF[2], Hoogeveen RC[3], Ballantyne CM[3], Basu S[4], Cushman M[5], Folsom AR[2].

Exogenous hormone treatments in women (oral contraceptives and hormone replacement therapy [HRT]) are established risk factors for venous thromboembolism (VTE), but less is known about associations between plasma levels of endogenous hormones and VTE risk. We examined the association of baseline dehydroepiandrosterone sulphate (DHEAS), testosterone and sex hormone-binding globulin (SHBG) with risk of future VTE in men and post-menopausal women in the Atherosclerosis Risk in Communities Study. Testosterone, DHEAS and SHBG were measured in plasma samples collected in 1996 to 1998. Cox proportional hazards models were used to estimate hazard ratios for incident VTE adjusting for age, race/ethnicity, body mass index, height, smoking, estimated glomerular filtration rate and C-reactive protein. All analyses were stratified by sex and by current HRT use in women. Among 3,051 non-HRT-using women, 1,414 HRT-using women and 3,925 men at risk at baseline, 184, 62 and 206 experienced incident VTE after a median follow-up of 17.6 years. Plasma hormones were not associated with incidence of VTE among men and non-HRT-using women, although lower plasma DHEAS, when modelled using quartiles or restricted cubic splines, was associated with higher risk of VTE among HRT-using women. This study does not support the existence of an important association between plasma concentrations of endogenous testosterone, DHEAS or SHBG with risk of VTE in middle-aged to older men or post-menopausal women not using HRT.

Effetti trombo-embolici della terapia con testosterone?

Review

Testosterone treatment and cardiovascular and venous thromboembolism risk: what is 'new'?

G Corona,[1] M Dicuio,[2,3] G Rastrelli,[4] E Maseroli,[4] F Lotti,[4] A Sforza,[1] M Maggi[4]

Available data do not support an increased VTE to TTh.

The previously reported cases of TTh-related VTE were frequently related to a previously undiagnosed thrombophilia-hypofibrinolysis status.

Hence, an anamnestic screening for thrombophilia before starting TTh is recommended, just as it is for the use of oral contraceptives.

Testosterone e carcinoma della prostata

Ruolo del testosterone nella patogenesi dell'ipertrofia prostatica benigna

1° HIT: infezione virale o batterica

2° HIT: sdr. plurimetabolica/ ipercolesterolemia

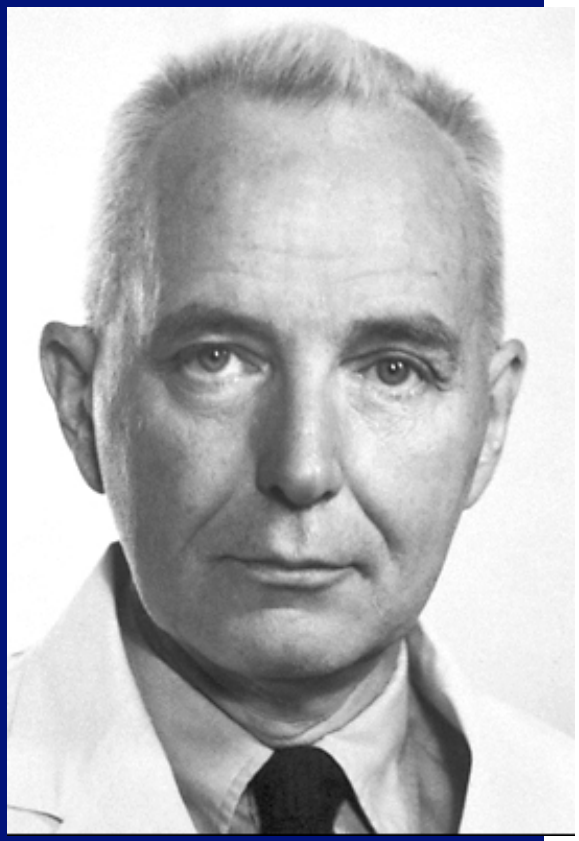
3° HIT: ipogonadismo/ iperestrogenismo

The combined action of all three hits, or even two of them, may result in overexpression of Toll-like receptors (TLRs), transformation of prostatic cells into antigen-presenting cells and activation of resident human prostate-associated lymphoid tissue ending in overproduction of growth factors which, in turn, will induce prostate remodeling and further prostate enlargement. The mechanical obstruction, along with the direct action of the unfavorable metabolic and hormonal milieu on the bladder neck, helps in generating LUTS.

Vignozzi L 2014 J Endocrinol Invest 37(4):313-22

Testosterone e carcinoma della prostata

Historically, the fear of testosterone "fueling" CaP comes from the work of Drs. Charles Huggins and Clarence Hodges, who found in 1941 that castration resulted in regression of metastatic CaP, solidifying the androgen-dependent model of CaP.



Studies on Prostatic Cancer

I. The Effect of Castration, of Estrogen and of Androgen Injection on Serum Phosphatases in Metastatic Carcinoma of the Prostate*

Charles Huggins, M.D., and Clarence V. Hodges, M.D.

(From the Department of Surgery, the University of Chicago, Chicago, Illinois)

(Received for publication March 22, 1941)

Carcinoma of the prostate gland is peculiarly favorable for endocrine investigation since frequent serial observations of the activity of phosphatases in serum were found to provide objective indices of activity of the neoplasm when the enzymes were increased in amount above normal. In the present paper data are given for the values of serum phosphatases in carcinoma of the prostate and in normal men. We shall demonstrate that the acid phosphatase of serum is reduced in metastatic carcinoma of the prostate by decreasing the activity of androgens through castration or estrogenic injections and that this enzyme is increased by injecting androgens. We have been unable to find previous observations indicating any relationship of hormones to carcinoma of the prostate gland.

An enzyme capable of hydrolyzing phosphoric esters was discovered by Grosser and Husler (4) in intestinal mucosa and kidney. Robison (16) found that this enzyme was particularly high in activity in growing bone and cartilage and that its activity was greatest at pH 9 to 9.5. This "alkaline phosphatase" was found by Kay (9) to be increased in the serum in certain bone diseases including metastasis of neoplasms to bone and later work has shown that among these conditions is carcinoma of the prostate.

Davies (3) and Bamann and Riedel (1) discovered that there occurs in the spleen and kidney of swine and cattle, in addition to the alkaline phosphatase, a phosphatase with an activity maximum at pH 4.8. An enzyme believed to be identical with this "acid phosphatase" was found by Kutscher and Wolbergs (11) to be present in very large amount in the human prostate gland. This finding of great activity of acid phosphatase in the prostate gland was confirmed and extended to include prostatic cancer by Gutman, Sproul, and Gutman (7). The serum of certain patients with disseminated prostatic carcinoma was found by Gutman and Gutman (6) and Barringer and Woodard (2) to exhibit increased acid phosphatase activity. Robinson, Gutman, and Gutman (15) summarized the acid phosphatase activity levels of 44 patients with carcinoma of the prostate. They concluded that a marked rise in acid phosphatase in serum is associated with the appearance or spread of roentgenologically demonstrable skeletal metastases and implies dissemination of the primary tumor and thus is of unfavorable prognostic significance.

* This investigation was aided by a grant from the Committee on Research in Problems of Sex, the National Research Council.

Methods and Materials

The phosphatase activity of serum was determined by the method of King and Armstrong (10) using 0.005 M disodium monophenylphosphate as substrate. The buffers used were 0.05 M barbital-sodium at pH 9.3, and 0.1 M Sörensen's citrate-HCl or Walpole's 0.2 N sodium acetate-acetic acid buffers at pH 5. All serums were tested in duplicate and were added directly to buffer-substrate solutions without dilution; they were incubated at 37.5° C. for 30 minutes. Precautions were observed that all solutions were at this temperature before testing. Blanks were run by adding the protein precipitant to the buffer-substrate solution before adding serum. Colorimetric procedures were carried out with the Evelyn photoelectric colorimeter using a 6600 A filter. The results are expressed in King and Armstrong units, a unit being defined as that degree of phosphatase activity which at pH 9.3 (or pH 5.0, respectively) and 37.5° C. will liberate 1 mgm. of phenol from the specified buffer-substrate solution in one-half hour.

Phosphatase determinations at pH 5 and 9.3 were made on the serum of 40 normal men, of 21 men with benign prostatic hypertrophy, and of 47 men with carcinoma of the prostate. The diagnosis of carcinoma of the prostate gland was derived from one or more of the following procedures: rectal palpation, cystoscopic examination, transurethral resection with microscopic examination, or roentgenologic evidence of skeletal metastases. Necropsy was obtained in 2 cases. All patients had x-ray studies of the bony pelvis.

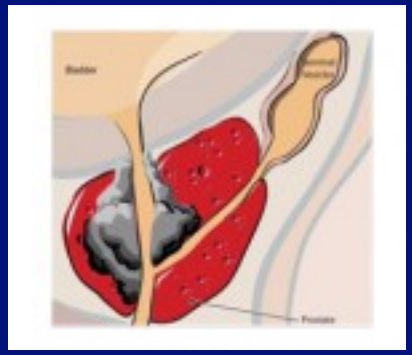
Eight patients who had carcinoma of the prostate with skeletal metastases and with moderate or great elevation of acid phosphatase of serum values above 20 units in 100 cc. were selected for intensive study in the hospital. Each patient also had elevation of alkaline phosphatase in the serum. Both of these enzymes were determined on the serum 3 times weekly for many weeks. Bilateral castration was carried out in all. Five patients were injected with stilbestrol, 1 mgm.

Testosterone e carcinoma della prostata

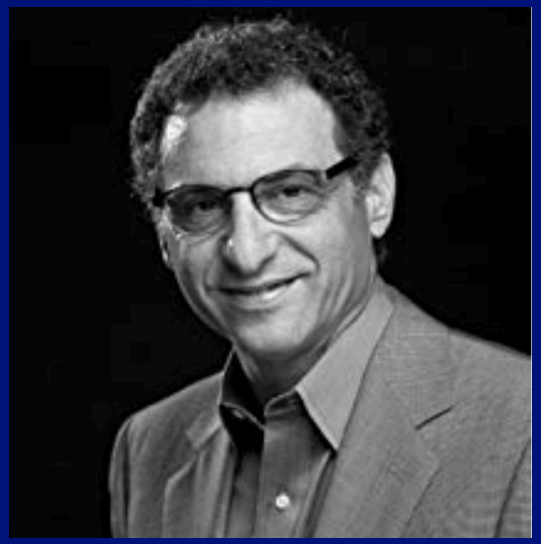
The 5-year survival rate for localized disease is nearly 100%, with a 10-year survival rate of 95%.

CaP survivors account for a large fraction of all cancer survivors, which has resulted from improvements in treatment, as well as an emphasis on quality of life after treatment.

Given the large number of older men who are living longer after CaP treatment, the incidence of hypogonadism in this population is also on the rise, raising important ethical and medical questions about treatment in these men.

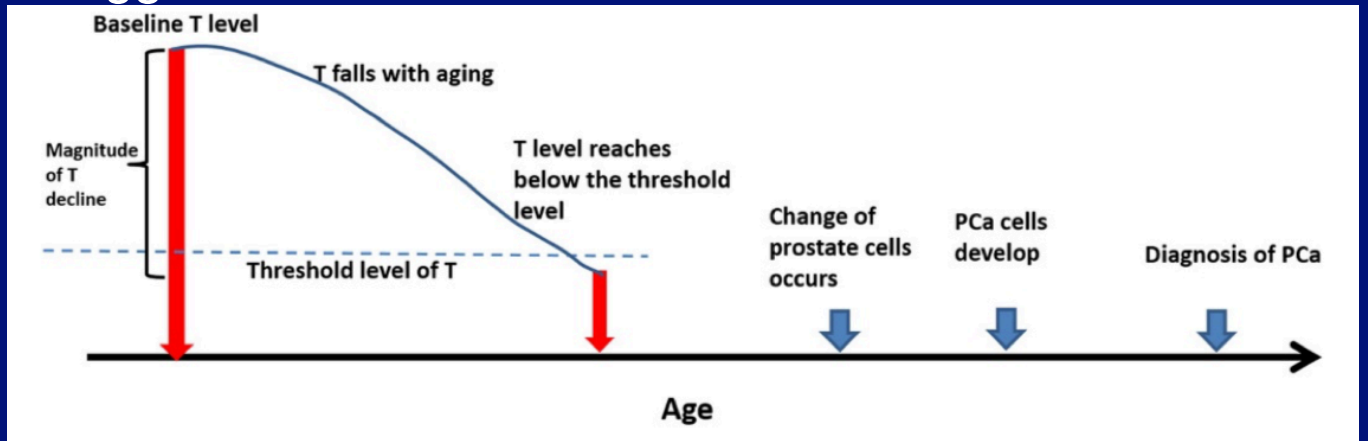


Basso Testosterone e carcinoma della prostata



The possibility that hypogonadism is more common in men with CaP was first proposed in 1996 by Morgentaler et al. when they reported a higher prevalence of biopsy-detectable CaP in men with low total or free testosterone levels.

Since then, the literature has yielded conflicting results on the relationship between endogenous testosterone levels and the development of CaP, though it generally supports the possibility that low testosterone is predictive of CaP and more aggressive disease.



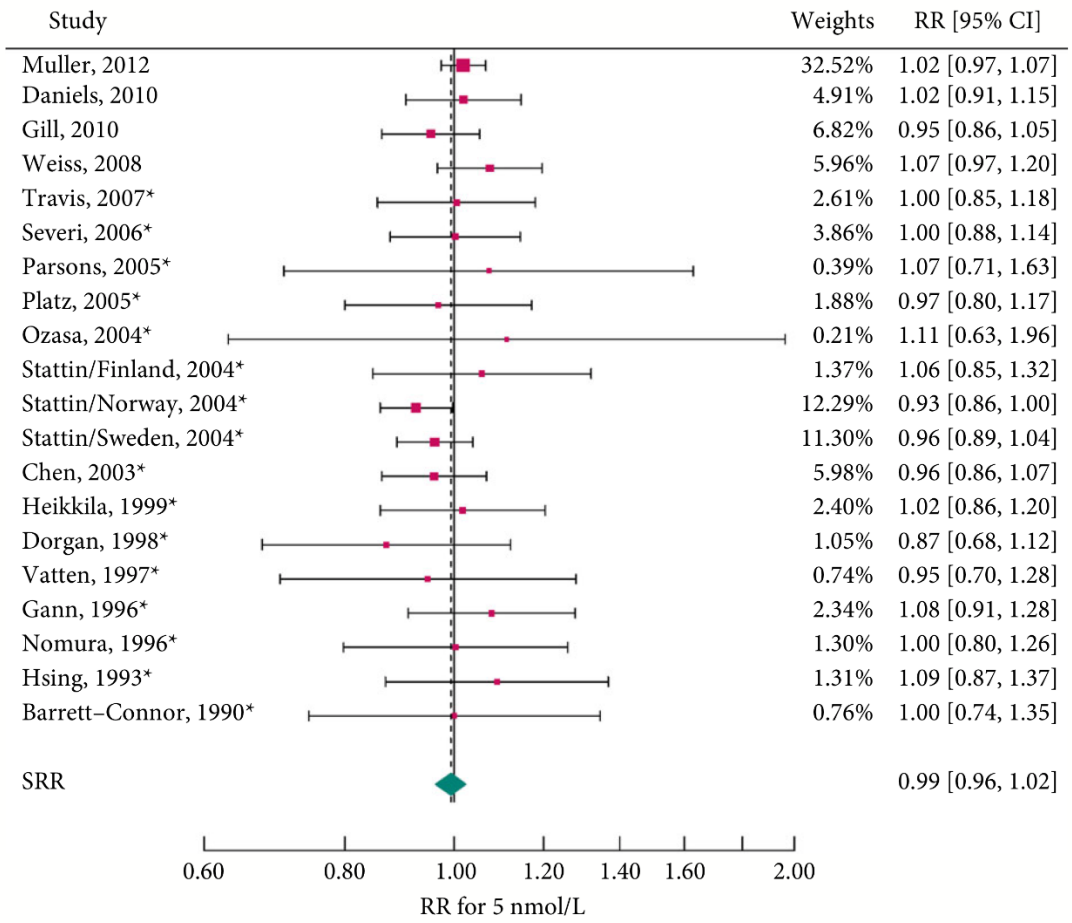
Testosterone e rischio di carcinoma della prostata: no aumento

BJUI

Endogenous and exogenous testosterone and the risk of prostate cancer and increased prostate-specific antigen (PSA) level: a meta-analysis

Peter Boyle*,†, Alice Koechlin*,†, Maria Bota*,†, Alberto d'Onofrio†, David G. Zaridze‡, Paul Perrin†, John Fitzpatrick§, Arthur L. Burnett¶,** and Mathieu Boniol*,†

Fig. 1 Serum testosterone and risk of prostate cancer (dose–response meta-analysis). EHPCCG, Endogenous Hormones and Prostate Cancer Collaborative Group; RR, relative risk; SRR, summary relative risk.



**: study included in EHPCCG pooled analysis*

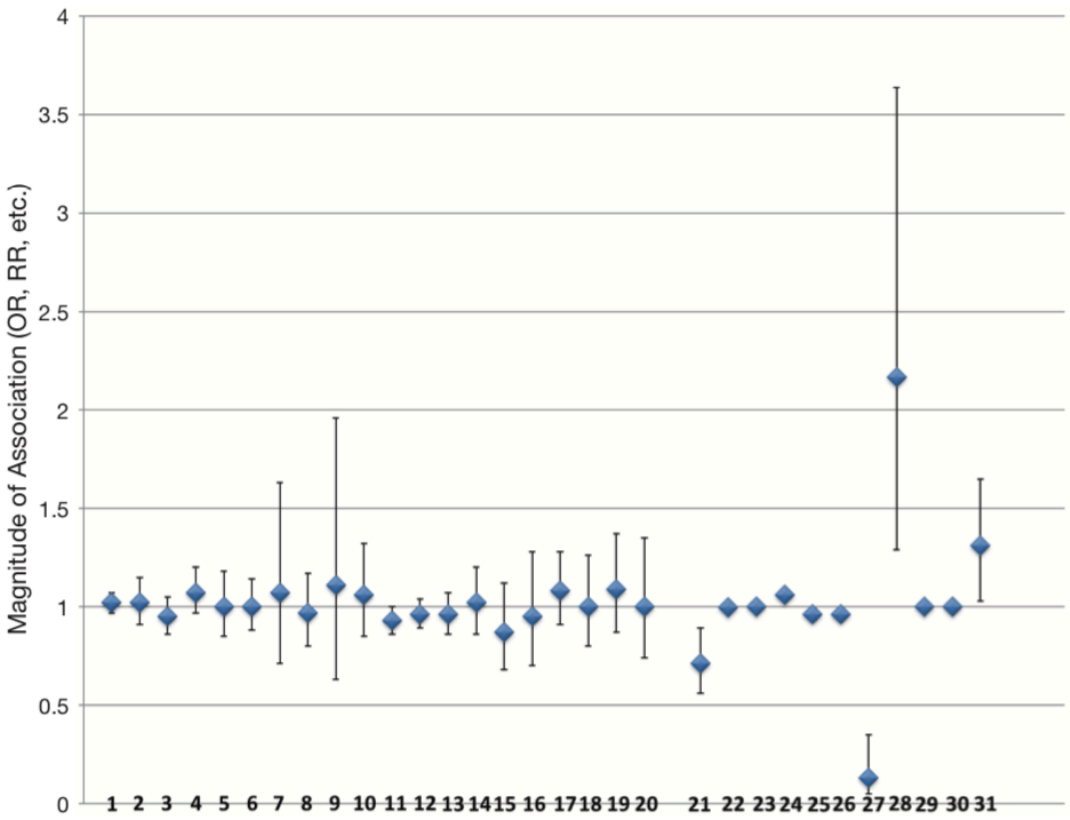
Heterogeneity: I^2 = 0% [0%; 19%]; Q = 12.20, df = 19 (p = 0.88)
Publication bias: Begg = 0.16 (p = 0.87); Egger = –0.79 (p = 0.17);
Macaskill = –0.41 (p = 0.69)

Testosterone e rischio di carcinoma della prostata: no aumento

Review Article

Endogenous and exogenous testosterone and prostate cancer: decreased-, increased- or null-risk?

David S. Lopez[1,2], Shailesh Advani[1], Konstantinos K. Tsilidis[3,4], Run Wang[2], Steven Canfield[2]



1	Muller *et al.* 2012 (25)
2	Daniels *et al.* 2010 (34)
3	Gill *et al.* 2010 (35)
4	Weiss *et al.* 2008 (36)
5	Travis *et al.* 2007 (37)
6	Severi *et al.* 2006 (38)
7	Parsons *et al.* 2005 (39)
8	Platz *et al.* 2005 (26)
9	Ozasa *et al.* 2004 (40)
10	Stattin (Finland) *et al.* 2004 (41)
11	Stattin (Norway) *et al.* 2004 (41)
12	Stattin (Sweden) *et al.* 2004 (41)
13	Chen *et al.* 2003 (42)
14	Heikkila *et al.* 1999 (43)
15	Dorgan *et al.* 1998 (44)
16	Vatten *et al.* 1997 (45)
17	Gann *et al.* 1996 (46)
18	Nomura *et al.* 1996 (47)
19	Hsing *et al.* 1993 (48)
20	Barrett-Connor *et al.* 1990 (49)
21	Mearini *et al.* 2013 (27)
22	Lane *et al.* 2008 (28)
23	Massengill *et al.* 2003 (29)
24	Salonia *et al.* 2011 (30) (ECE)
25	Salonia *et al.* 2011 (30) (SVI)
26	Salonia *et al.* 2011 (30) (HGPCa)
27	Karamanolakis *et al.* 2006 (31)
28	Imamoto *et al.* 2005 (32)
29	Muller *et al.* 2012 (25) (Gleason 2-6)
30	Muller *et al.* 2012 (25) (Gleason 7-10)
31	Yano *et al.* 2007 (33)

Figure 1 Serum testosterone (continuous and 5 nmol/L increments) in observational studies (prospective, retrospective) and its effects on PCa events (stage and grade). Studies/analyses only show multivariable analyses to minimize confounding effects. Magnitudes of association (ORs, RRs, etc.) and 95% CIs (25-49). PCa, prostate cancer; OR, odds ratio; RR, relative risk.

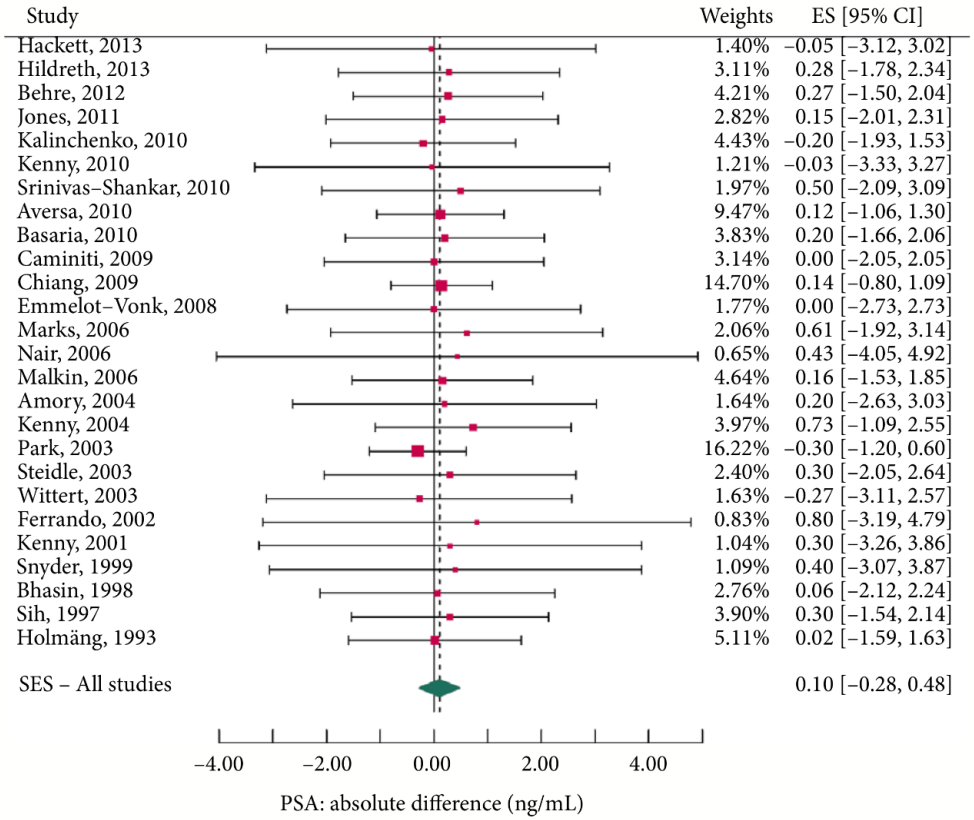
Terapia con Testosterone e PSA: no aumento

BJUI
BJU International

Endogenous and exogenous testosterone and the risk of prostate cancer and increased prostate-specific antigen (PSA) level: a meta-analysis

Peter Boyle*,†, Alice Koechlin*,†, Maria Bota*,†, Alberto d'Onofrio†, David G. Zaridze‡, Paul Perrin§, John Fitzpatrick¶, Arthur L. Burnett** and Mathieu Boniol*,†

Fig. 2 Testosterone replacement therapy (all forms) and absolute difference in PSA levels.



SES: Summary effect size

Heterogeneity: I^2 = 0% [0%; 0%]; Q = 2.03, df = 25 (p = 1.00)
Publication bias: Begg = 0.15 (p = 0.88); Egger = 0.48 (p = 0.01); Macaskill = 0.65 (p = 0.52)

Terapia con Testosterone e rischio di carcinoma della prostata: no aumento

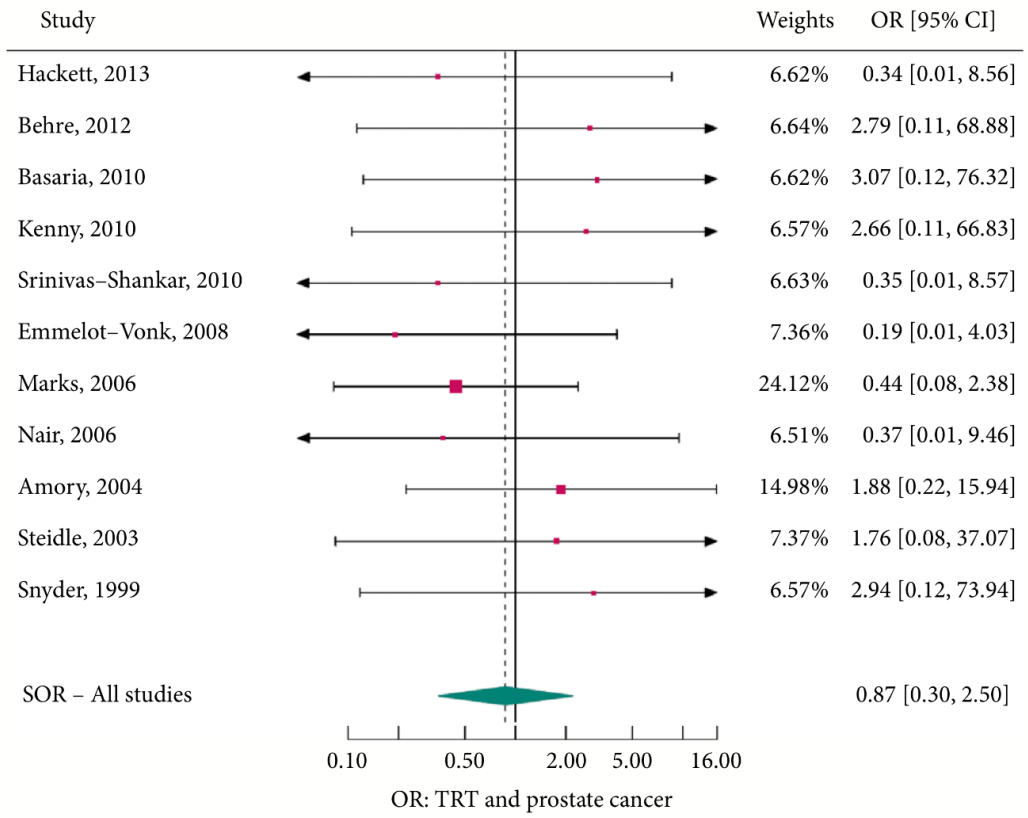
Although available studies do not support a link between TTh and prostate-specific antigen (PSA) levels or development/progression of CaP, careful monitoring of prostate size and serum PSA levels is recommended.

Fig. 3 Testosterone replacement therapy and risk of prostate cancer. OR, odds ratio.

BJUI
BJU International

Endogenous and exogenous testosterone and the risk of prostate cancer and increased prostate-specific antigen (PSA) level: a meta-analysis

Peter Boyle*,†, Alice Koechlin*,†, Maria Bota*,†, Alberto d'Onofrio†, David G. Zaridze‡, Paul Perrin§, John Fitzpatrick¶, Arthur L. Burnett** and Mathieu Boniol*,†



SOR: Summary odds ratio

Heterogeneity: I^2 = 0% [0%; 25%]; Q = 5.29, df = 10 (p = 0.87)
Publication bias: Begg = 0.23 (p = 0.82); Egger = 0.93 (p = 0.26); Macaskill = 0.40 (p = 0.70)

Terapia con Testosterone e rischio di carcinoma della prostata

Review Article

Endogenous and exogenous testosterone and prostate cancer: decreased-, increased- or null-risk?

David S. Lopez[1,2], Shailesh Advani[1], Konstantinos K. Tsilidis[3,4], Run Wang[2], Steven Canfield[2]

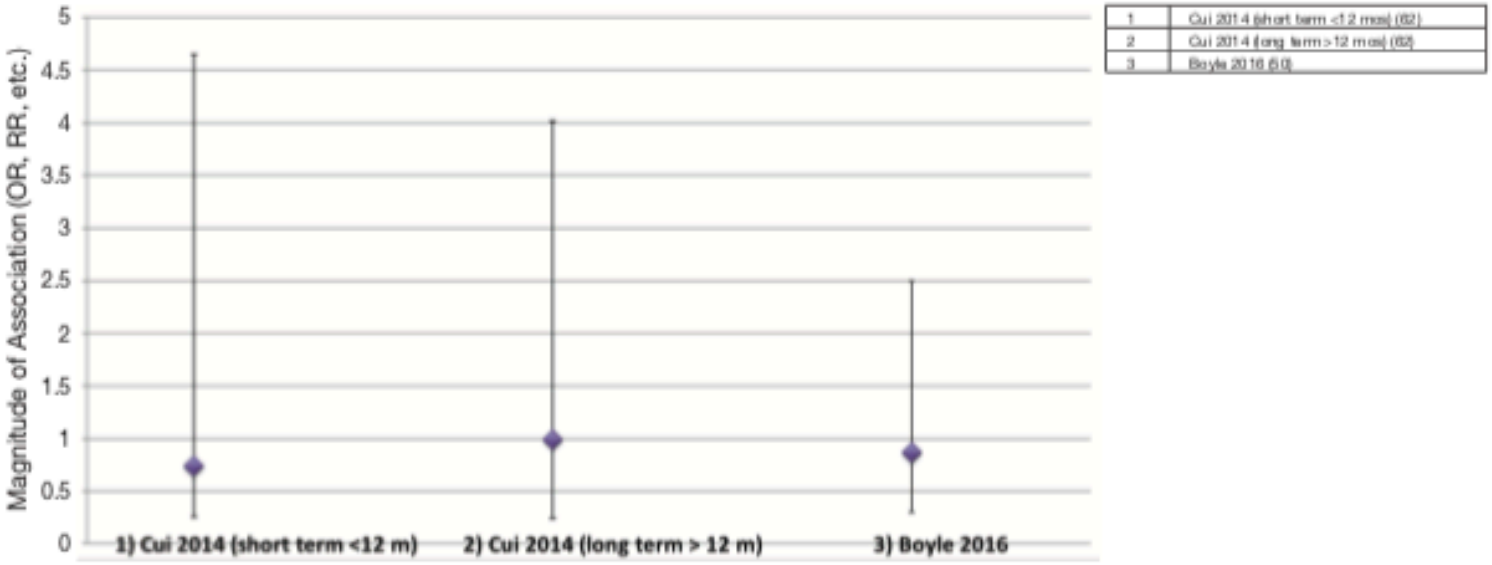


Figure 3 Meta-analyses of randomized controlled trials (RCTs) that investigated the effect of TTh on PCa events (stage and grade). Studies/analyses only show multivariable analyses to minimize confounding effects. Magnitudes of association (ORs, RRs, etc.) and 95% CIs (50,62). TTh, testosterone therapy; PCa, prostate cancer; OR, odds ratio; RR, relative risk.

Basso Testosterone e carcinoma della prostata: peggiore prognosi

Both low as well as high serum TT levels indicate Prostate Cancer poor prognosis

Anticancer Res. 2017 Oct;37(10):5559-5564.

Both High and Low Serum Total Testosterone Levels Indicate Poor Prognosis in Patients with Prostate Cancer.

Izumi K1, Shigehara K2, Nohara T2, Narimoto K2, Kadono Y2, Mizokami A2.

BACKGROUND/AIM:
Androgen-androgen receptor (AR) signal is known as a powerful driver of prostate cancer progression. We previously reported the limitation of prostate-specific antigen (PSA) at diagnosis as a prognostic biomarker of prostate cancer. Although serum total testosterone (TT) level has been reported as a prognostic biomarker for prostate cancer, its usability is still controversial. We examined the potential and characteristics of TT as a biomarker.

PATIENTS AND METHODS:
Serum TT levels of patients who underwent prostate biopsy were measured, and prostate cancer-specific survival (PCaSS), overall survival (OS), and the correlation between staging and serum TT level were analyzed.

RESULTS:
Of 379 biopsied patients, 255 were diagnosed with prostate cancer. The patients were divided into five groups according to their serum TT levels; patients with serum TT levels of <2 or ≥8 ng/ml (ENDs) had worse PCaSS and OS compared with those with middle serum TT levels between 2 and 8 ng/ml (MIDs). Moreover, ENDs showed a tendency of having castration-resistant cancer with advanced stage (T4 or N1 or M1). The TNM stage in ENDs was significantly higher than in MIDs.

CONCLUSION:
Although low serum TT level has been reported to indicate worse outcome in patients with prostate cancer, this study showed that both low as well as high serum TT levels indicate poor prognosis.

Basso Testosterone e carcinoma della prostata: grading

ONCOLOGY LETTERS 13: 1949-1957, 2017

Low serum testosterone is associated with tumor aggressiveness and poor prognosis in prostate cancer

HUAKANG TU[1], JIAN GU[1], QING H. MENG[2], JERI KIM[3], SARA STROM[1], JOHN W. DAVIS[4], YONGGANG HE[5], ELIZABETH A. WAGAR[2], TIMOTHY C. THOMPSON[3], CHRISTOPHER J. LOGOTHETIS[3] and XIFENG WU[1]

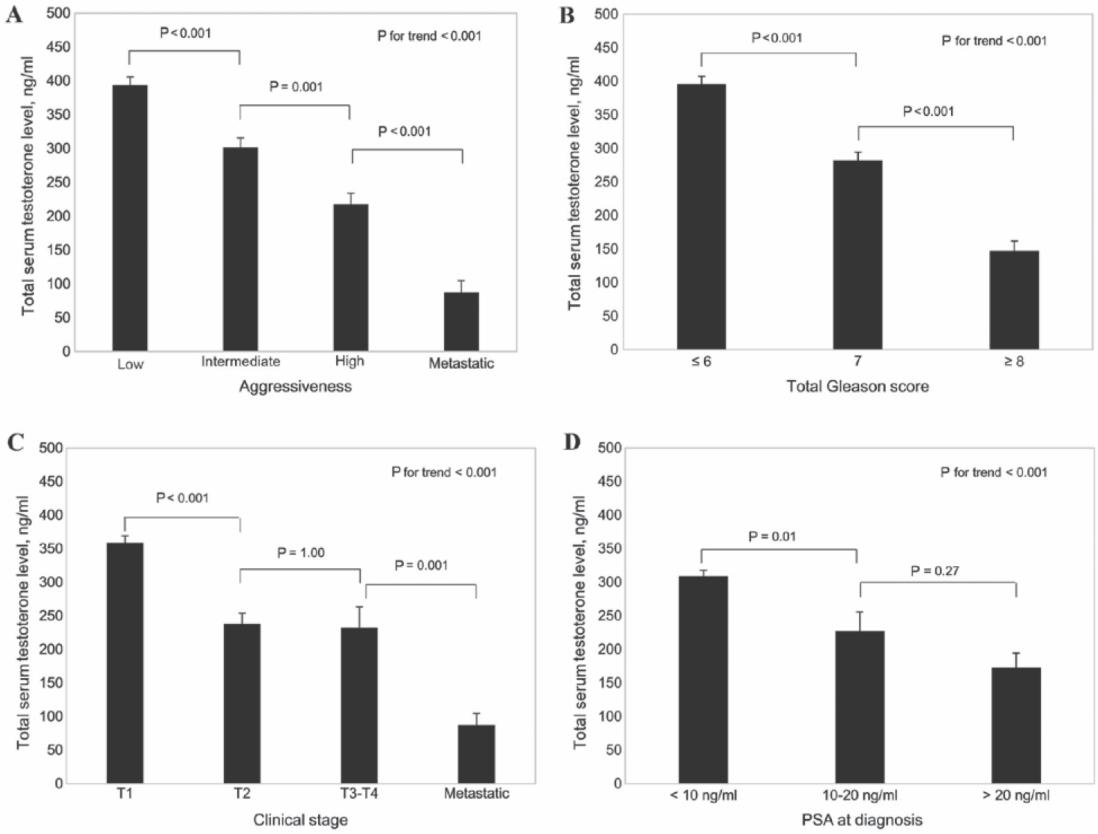


Figure 1. Association between total serum testosterone levels in patients with prostate cancer and (A) tumor aggressiveness, (B) total Gleason score, (C) clinical stage of tumor and (D) PSA levels at diagnosis. Results are presented as the mean ± standard error. PSA, prostate-specific antigen.

Basso Testosterone e carcinoma della prostata: stadio

ONCOLOGY LETTERS 13: 1949-1957, 2017

Low serum testosterone is associated with tumor aggressiveness and poor prognosis in prostate cancer

HUAKANG TU[1], JIAN GU[1], QING H. MENG[2], JERI KIM[3], SARA STROM[1], JOHN W. DAVIS[4], YONGGANG HE[5], ELIZABETH A. WAGAR[2], TIMOTHY C. THOMPSON[3], CHRISTOPHER J. LOGOTHETIS[3] and XIFENG WU[1]

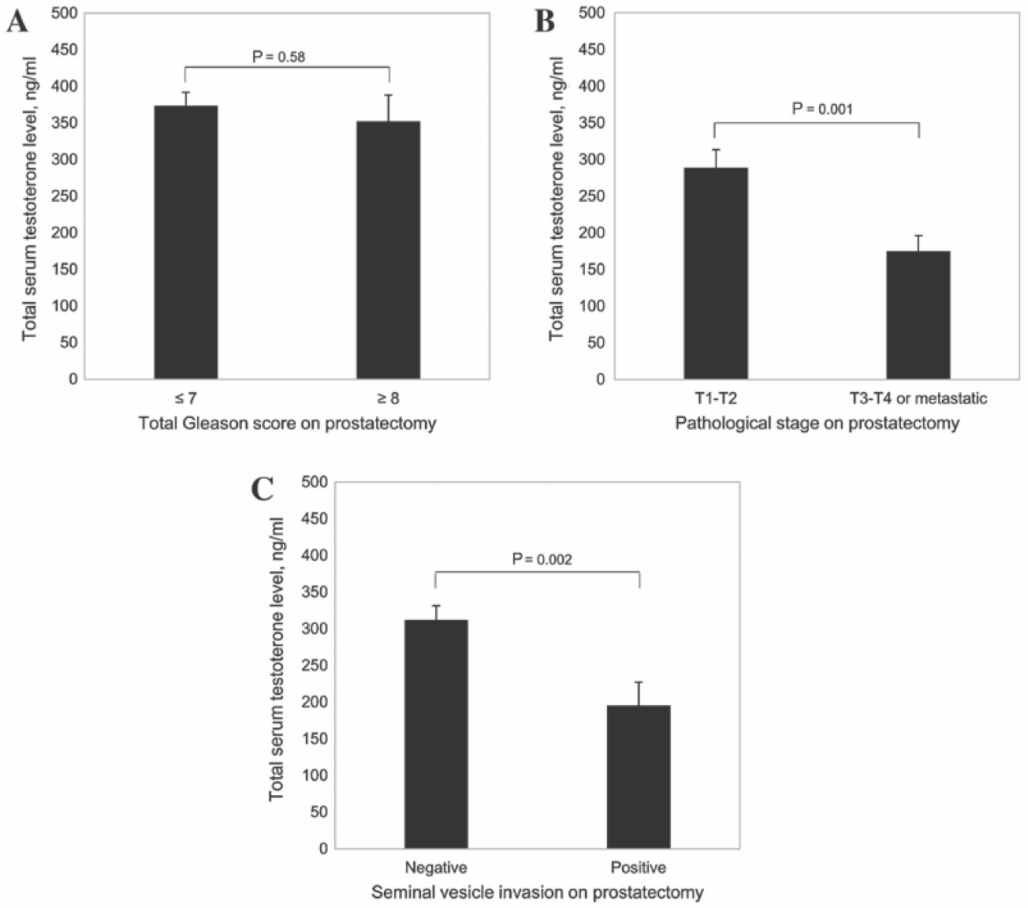


Figure 2. Association between total serum testosterone levels in patients with PCa who underwent radical prostatectomy and (A) total Gleason score, (B) pathological stage of the tumor and (C) seminal vesicle invasion. Results are presented as the mean ± standard error.

Basso Testosterone e carcinoma della prostata: sopravvivenza

ONCOLOGY LETTERS 13: 1949-1957, 2017

Low serum testosterone is associated with tumor aggressiveness and poor prognosis in prostate cancer

HUAKANG TU[1], JIAN GU[1], QING H. MENG[2], JERI KIM[3], SARA STROM[1], JOHN W. DAVIS[4], YONGGANG HE[5], ELIZABETH A. WAGAR[2], TIMOTHY C. THOMPSON[3], CHRISTOPHER J. LOGOTHETIS[3] and XIFENG WU[1]

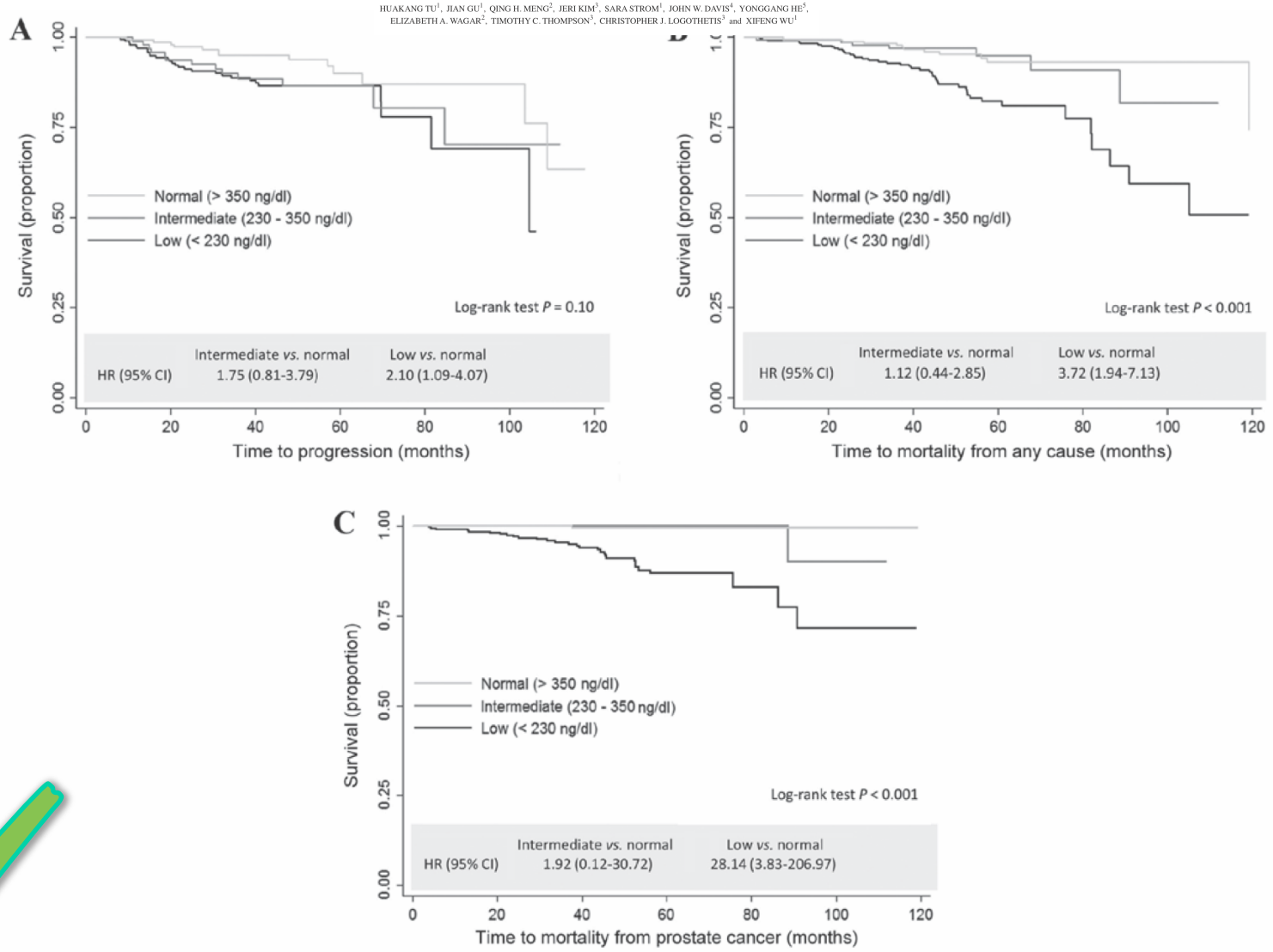


Figure 4. Unadjusted Kaplan-Meier estimator survival curves and HRs for the association between total serum testosterone levels and (A) disease progression, (B) mortality from all causes and (C) mortality due to prostate cancer. HR, hazard ratio; CI, confidence interval.

Basso Testosterone e carcinoma della prostata: recidiva

Low testosterone levels are not only associated with biochemically different tumors, but also a significantly altered clinical course.

Salonia et al. examined a cohort of 724 men with low- (34.7%), intermediate- (43.9%), or high-risk (21.4%) prostate cancer and observed that men with both the lowest and highest serum testosterone levels were at increased risk for prostate cancer recurrence after radical prostatectomy (p = 0.03).

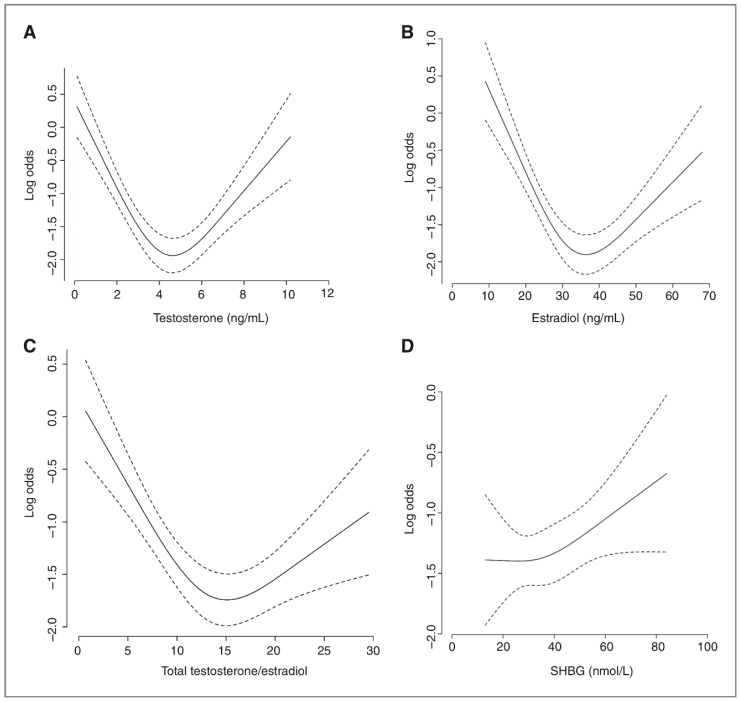


Figure 1. A–C, the relationship between serum tT levels (ng/mL), E_2 levels (pg/mL), and tT–E_2 values and high-risk prostate cancer at radical prostatectomy, respectively. The *y*-axis represents the risk (logarithmic scale) of high-risk prostate cancer at radical prostatectomy. In this context, high-risk prostate cancer was significantly more frequent both for the lowest and the highest circulating levels of serum tT and E_2 (all $P \leq 0.03$), depicting a nonlinear U-shaped risk behavior (A and B). Similar behavior was observed for the relationship between tT–E_2 values and high-risk prostate cancer (all $P < 0.001$; C). D, the relationship between serum SHBG levels (nmol/L) and high-risk prostate cancer at radical prostatectomy. The *y*-axis represents the risk (logarithmic scale) of high-risk prostate cancer at radical prostatectomy.

Imaging, Diagnosis, Prognosis

Clinical Cancer Research

Serum Sex Steroids Depict a Nonlinear U-Shaped Association with High-Risk Prostate Cancer at Radical Prostatectomy

Andrea Salonia, Firas Abdollah, Umberto Capitanio, Nazareno Suardi, Alberto Briganti, Andrea Gallina, Renzo Colombo, Matteo Ferrari, Giulia Castagna, Patrizio Rigatti, and Francesco Montorsi

Alto Testosterone e carcinoma della prostata: no effetti sulla comparsa, dubbi effetti su aggressività, positivi su recidiva

Several studies have reported no relationship, or even a protective relationship between high testosterone levels and the development of CaP.

The Reduction by Dutasteride of Prostate Cancer Events (REDUCE) trial reported a lack of association between normal or high testosterone levels and CaP incidence.

Urology. 2011 Sep;78(3):641-6. doi: 10.1016/j.urology.2011.03.063. Epub 2011 Jul 20.

Dutasteride improves outcomes of benign prostatic hyperplasia when evaluated for prostate cancer risk reduction: secondary analysis of the REduction by DUtasteride of prostate Cancer Events (REDUCE) trial.

Roehrborn CG1, Nickel JC, Andriole GL, Gagnier RP, Black L, Wilson TH, Rittmaster RS.

OBJECTIVE:

To investigate the effect of dutasteride versus placebo on the symptoms and associated complications of male lower urinary tract symptoms and benign prostatic hyperplasia (BPH) across a range of prostate volumes and BPH symptoms in men evaluated for prostate cancer risk reduction in the 4-year REduction by DUtasteride of prostate Cancer Events (REDUCE) trial.

METHODS:

REDUCE was a multicenter, randomized, double-blind, placebo-controlled study of prostate cancer risk reduction with daily dutasteride 0.5 mg or placebo. Eligible men were aged 50-75 years, with a prostate-specific antigen level of 2.5-10 ng/mL and a prostate volume of ≤80 cm3. The prespecified and post hoc analyses were performed on the incidence of acute urinary retention, BPH-related surgery, and urinary tract infections, as well as on changes in prostate volume, International Prostate Symptom Score, BPH Impact Index, and maximal urinary flow rate (Qmax).

RESULTS:

A total of 8122 men were included in the efficacy population. During the 4-year study, the International Prostate Symptom Score increased in placebo-treated patients, while dutasteride-treated patients had a stabilized or decreased International Prostate Symptom Score and improved BPH Impact Index and quality of life due to urinary symptom scores across all prostate volume quintiles (including prostate glands smaller than those studied in previous dutasteride trials). 48 months, the incidence of acute urinary retention or BPH-related surgery was significantly less in the dutasteride group (2.5%) than in the placebo group (9%) overall (P<.001) and in each baseline prostate volume quintile (P<.01).

CONCLUSION:

During the 4-year study, dutasteride was associated with a decreased risk of BPH progression in men with mild-to-moderate symptoms and normal or enlarged prostates

Alto Testosterone e carcinoma della prostata: no effetti sulla comparsa, dubbi effetti su aggressività, positivi su recidiva

As with low testosterone, there is evidence that men with high testosterone have differing tumor characteristics from men with normal testosterone. Several studies have reported differing Gleason scores for these men.

A 2014 retrospective analysis of 220 men who underwent RP observed that men with higher pretreatment testosterone levels (T > 447 ng/dL) had a higher risk of Gleason sum ≥ 8 disease (p = 0.0004) when compared to men with lower testosterone levels.

Porcaro AB, Petrozziello A, Ghimenton C, Migliorini F, Sava T, Caruso B, et al. Associations of pretreatment serum total testosterone measurements with pathology-detected Gleason score cancer. Urol Int. 2014;93(3):269–78.

Though Platz et al. reported no difference in CaP rates as a function of baseline testosterone level, they did report that higher total testosterone level was positively associated with Gleason sum < 7 disease and inversely associated with Gleason sum ≥ 7 disease.

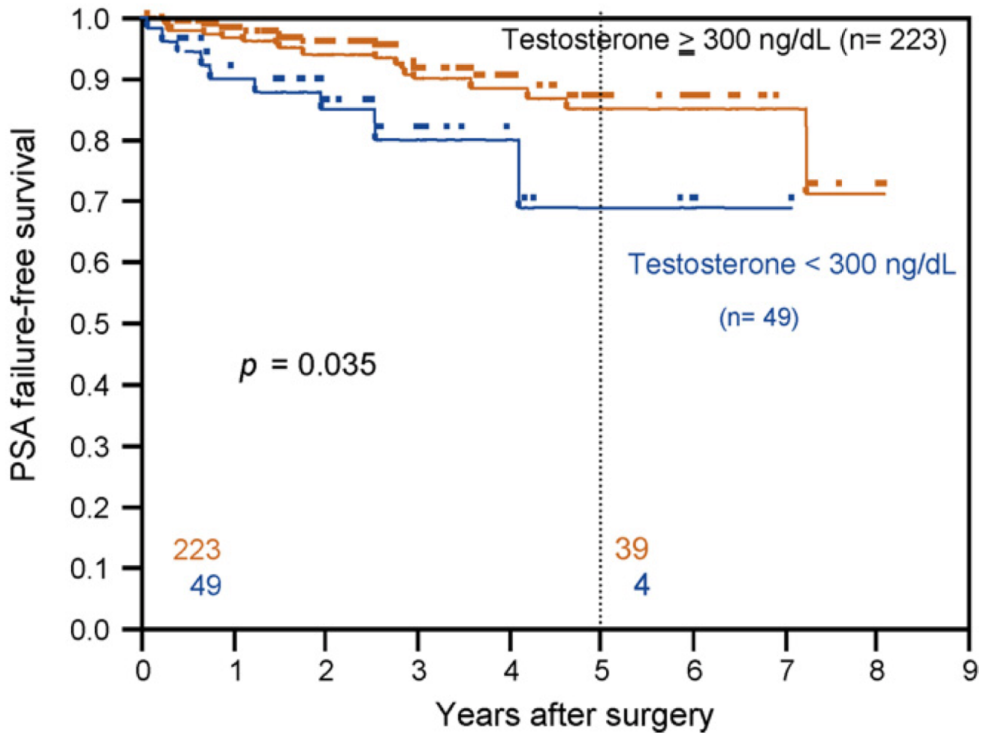
Platz EA, et al. Sex steroid hormones and the androgen receptor gene CAG repeat and subsequent risk of prostate cancer in the prostate-specific antigen era. Cancer Epidemiol Biomark Prev. 2005;14(5):1262–9.

In 2016, Porcaro et al. found that high testosterone levels predicted an increased risk of Gleason score upgrading (OR 1.06; p = 0.027) [38].

Porcaro AB, Petroziello A, Brunelli M, de Luyk N, Cacciamani G, Corsi P, et al. High testosterone preoperative plasma levels independently predict biopsy Gleason score upgrading in men with prostate cancer undergoing radical pr... Int. 2016;96(4):470– 8.

Alto Testosterone e carcinoma della prostata: effetti positivi su recidiva

A larger cohort confirmed results from earlier studies suggesting high testosterone to be protective against recurrence.




EUROPEAN UROLOGY 52 (2007) 696–701

available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Prostate Cancer

Preoperative Serum Testosterone Level as an Independent Predictor of Treatment Failure following Radical Prostatectomy

Shinya Yamamoto [a,*], Junji Yonese [a], Satoru Kawakami [a], Yuhei Ohkubo [a], Manabu Tatokoro [a], Yoshinobu Komai [a], Hideki Takeshita [a], Yuichi Ishikawa [b], Iwao Fukui [a]

Fig. 1 – Kaplan-Meier prostate-specific antigen (PSA) failure–free survival curves according to preoperative testosterone level (normal testosterone group: orange line; low testosterone group: blue line). Numbers of patients at risk are shown on horizontal axis at 0 and 5 yr.

Testosterone e carcinoma della prostata: saturazione del recettore androgenico

Important for the discussion of the relationship between TTh and CaP, however, is the androgen receptor (AR) saturation point.

This is the point above which no further increases in PSA and is estimated to be at a serum testosterone concentration of 150–200 ng/dL in humans.

Theoretically, this is also the point at which testosterone would stop "fueling" CaP, though this has not been definitively proven in humans.

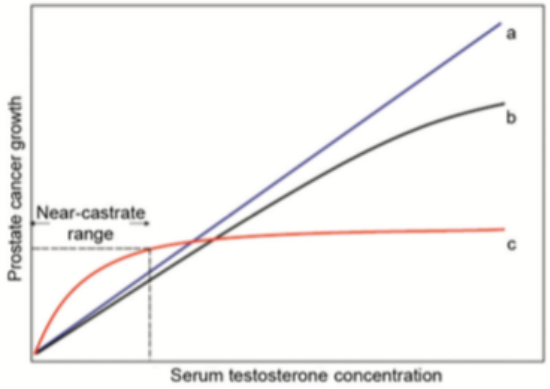


Figure 1: Proposed saturation model for the relationship of prostate cancer (PCa) growth and serum T concentration. The traditional belief has been that higher T concentration caused increasing rates of PCa growth, as represented by curves a and b. All available evidence demonstrates a powerful effect of T on PCa growth at low T concentration, yet little or no effect above the near-castrate range. The proposed model for the relationship between T and PCa is thus shown as curve c and is consistent with a saturation model, as seen in many other biologic systems. From Morgentaler.[13]

Morgentaler A 2015 AJA 17:206-211

Terapia con Testosterone e sviluppo del carcinoma della prostata

At lower concentrations than the optimal androgen level, increasing androgen concentration promoted the proliferation of PCa cells. However, at the higher concentrations, increasing androgen concentration resulted in a dose-dependent proliferative inhibition.

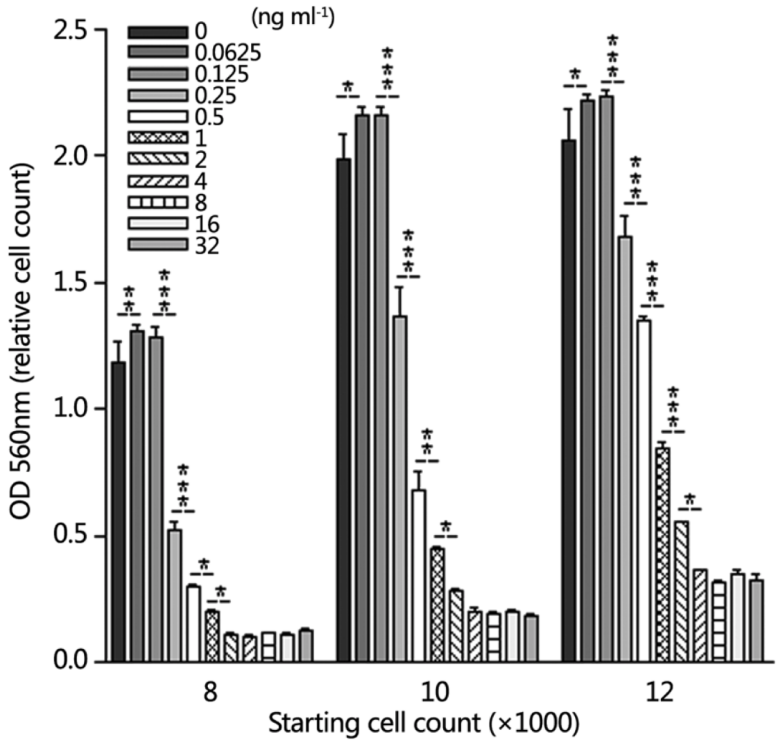
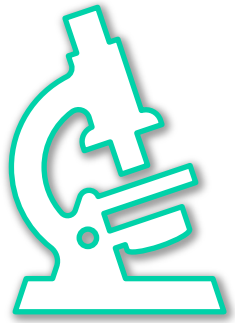


Figure 1: Effect of testosterone on the growth of LNCaP cells in regular medium. Eight thousand, ten thousand, or twelve thousand cells per well were seeded in medium supplemented with 10% regular fetal bovine serum and the cells were treated with various levels of testosterone for 10 days. The stars represent the statistic difference between each two groups. *$P<0.05$, **$P<0.01$, ***$P<0.001$.



Asian Journal of Andrology (2014) 16, 864–868
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www.asiaandro.com; www.ajandrology.com

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ORIGINAL ARTICLE

Prostate Cancer

Physiological normal levels of androgen inhibit proliferation of prostate cancer cells *in vitro*

Weitao Song, Mohit Khera

Prostate saturation model in vivo

EUROPEAN UROLOGY 50 (2006) 935–939

available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Review – Andrology

Testosterone and Prostate Cancer: An Historical Perspective on a Modern Myth

Abraham Morgentaler *

The prostate saturation model was proposed by Morgentaler and Traish to explain the association between prostate tissue growth and androgen stimulation, particularly at lower serum testosterone levels.

This theory proposes that prostate tissue is only sensitive to androgens until the AR saturation point is reached.

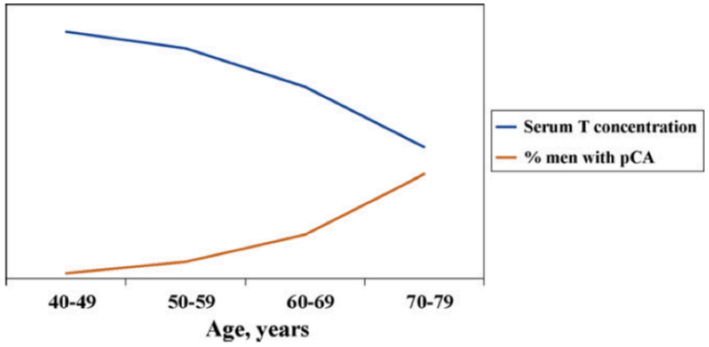


Fig. 1 – Prostate cancer prevalence and testosterone levels with ageing. pCA: prostate cancer, T: testosterone.

Prostate saturation model in vivo: volontari sani

One of the first studies to support the androgen saturation theory was published in 1998 by Cooper et al. The authors found that healthy volunteers who received TTh experienced only a rise in testosterone over 15 weeks and no rise in prostate volume or serum PSA levels at any dose of exogenous testosterone

J Urol. 1998 Feb;159(2):441-3.

Effect of exogenous testosterone on prostate volume, serum and semen prostate specific antigen levels in healthy young men.

Cooper CS1, Perry PJ, Sparks AE, MacIndoe JH, Yates WR, Williams RD.

PURPOSE:

We investigate and define the effects of exogenous testosterone on the normal prostate.

MATERIALS AND METHODS:

A total of 31 healthy volunteers 21 to 39 years old were randomized to receive either 100, 250 or 500 mg. testosterone via intramuscular injection once a week for 15 weeks. Baseline measurements of serum testosterone, free testosterone and prostate specific antigen (PSA) were taken at week 1. Semen samples were also collected for PSA content and prostate volumes were determined by transrectal ultrasound before testosterone injection. Blood was then drawn every other week before each testosterone injection for the 15 weeks, every other week thereafter until week 28 and again at week 40. After the first 15 weeks semen samples were again collected, and prostate volumes were determined by repeat transrectal ultrasound.

RESULTS:

Free and total serum testosterone levels increased significantly in the 250 and 500 mg. dose groups. No significant change occurred in the prostate volume or serum PSA levels at any dose of exogenous testosterone. Total semen PSA levels decreased following administration of testosterone but did not reach statistical significance.

CONCLUSIONS:

Despite significant elevations in serum total and free testosterone, healthy young men do not demonstrate increased serum or semen PSA levels, or increased prostate volume in response to exogenous testosterone injections.

Prostate saturation model in vivo: ipogonadici

A double-blind placebo-controlled study of 274 hypogonadal men concluded that testosterone resulted in a predictable increase in PSA during treatment, but only when the baseline testosterone level was < 250 ng/dL. No significant variation in PSA levels in men with baseline testosterone > 250 ng/dL was observed

J Sex Med. 2014 Nov;11(11):2818-25. doi: 10.1111/jsm.12657. Epub 2014 Aug 18.

Factors influencing prostate-specific antigen response among men treated with testosterone therapy for 6 months.

Morgentaler A1, Benesh JA, Denes BS, Kan-Dobrosky N, Harb D, Miller MG.

INTRODUCTION:
Factors influencing prostate-specific antigen (PSA) changes in men undergoing testosterone (T) therapy have not been well studied.
AIM:
The aim of this study was to assess the influence of selected variables on PSA changes in hypogonadal men administered with 1.62% testosterone gel (T-gel) for 6 months.
METHODS:
A double-blind, placebo-controlled study of 274 (234 T-gel, 40 placebo) hypogonadal men >18 years of age, with baseline T concentrations <300 ng/dL, PSA ≤2.5 ng/mL, and negative digital rectal examination. Subjects received once-daily T-gel for T therapy.
MAIN OUTCOME MEASURES:
Changes in mean serum PSA, percentage of free PSA (%fPSA), and T from baseline to 6 months (182 days).
RESULTS:
Mean age was 53.5 years and baseline mean values were total T 247 ng/dL, PSA 0.9 ng/mL, and %fPSA 24.6%. Among men treated with T-gel, T increased to 499 ng/dL and PSA increased by 0.1 ng/mL (P = 0.0012). PSA increased ≥0.3 ng/mL in 26.3%, <0.3 ng/mL in 73.7%, including a decline from baseline in 33.0%. In the placebo group, T increased 29 ng/dL to 274 ng/dL, and PSA decreased 0.1 ng/mL, compared with baseline. A greater increase in PSA was noted in men ≥60 years old than in men <60 years old (0.4 vs. 0.05 ng/mL, respectively; P = 0.0006). Mean PSA did not change in men with baseline serum T >250 ng/dL, whereas it increased by 0.2 ng/mL in men with T ≤250 ng/dL (P = 0.0031). PSA increased 0.3 ng/mL in men with baseline %fPSA <20% and 0.1 ng/mL in men with %fPSA ≥20%.
CONCLUSIONS:
Overall, T-gel treatment was associated with a minor increase in PSA, of questionable clinical significance. Factors predicting greater PSA increases included age ≥60 years, baseline T ≤250 ng/dL, and %fPSA <20%. Men with T >250 ng/dL and age <60 years demonstrated minimal or no PSA change.

Terapia con Testosterone e sviluppo del carcinoma della prostata

While multiple studies support an increased risk of CaP in hypogonadal men, there are fewer data on whether TTh reverses this risk.

A meta-analysis analyzed all studies examining the risk of CaP in older men on TTh between 1966 and 2004.

Nineteen studies were identified that included 651 men given TTh and 433 controls. The combined rate of all prostate-related events was higher in the TTh group (OR = 1.78, 95% confidence interval [CI], 1.07–2.95).

Rates of CaP and PSA > 4 ng/mL were higher in the TTh group, though these were not statistically significant.

J Gerontol A Biol Sci Med Sci. 2005 Nov;60(11):1451-7.
Adverse events associated with testosterone replacement in middle-aged and older men: a meta-analysis of randomized, placebo-controlled trials.
Calof OM1, Singh AB, Lee ML, Kenny AM, Urban RJ, Tenover JL, Bhasin S.

Terapia con Testosterone e sviluppo del carcinoma della prostata

553 men — 42 treated and 162 untreated hypogonadal men and 349 eugonadal men.
The incidence of positive prostate biopsies was lowest in hypogonadal men on TTh. These men also had significantly lower grade and stage of CaP.

Aging Male. 2017 Jun;20(2):125-133. doi: 10.1080/13685538.2017.1298584. Epub 2017 Mar 10.
Is there a protective role of testosterone against high-grade prostate cancer? Incidence and severity of prostate cancer in 553 patients who underwent prostate biopsy: a prospective data register.
Yassin A1,2,3, Salman M1, Talib RA4, Yassin DJ1,2.

(Canadian health databases) 10,311 men treated with TTh and 28,029 controls over a 5-year span and found that men in the long-term TTh group had a lower incidence of CaP and mortality when compared to the hypogonadal group (HR 0.60, 95% CI 0.45–0.80).

Lancet Diabetes Endocrinol. 2016 Jun;4(6):498-506. doi: 10.1016/S2213-8587(16)00112-1. Epub 2016 May 7.
Survival and cardiovascular events in men treated with testosterone replacement therapy: an intention-to-treat observational cohort study.
Wallis CJ1, Lo K2, Lee Y3, Krakowsky Y1, Garbens A1, Satkunasivam R1, Herschorn S1, Kodama RT1, Cheung P4, Narod SA5, Nam RK6.

Terapia con Testosterone e sviluppo del carcinoma della prostata

BJUI
BJU International

Testosterone treatment is not associated with increased risk of prostate cancer or worsening of lower urinary tract symptoms: prostate health outcomes in the Registry of Hypogonadism in Men

Frans M.J. Debruyne*, Hermann M. Behre†, Claus G. Roehrborn‡, Mario Maggi§, Frederick C.W. Wu¶, Fritz H. Schröder**, Thomas Hugh Jones††, Hartmut Porst‡‡, Geoffrey Hackett§§, Olivia A. Wheaton¶¶, Antonio Martin-Morales***, Eric J. Meuleman†††, Glenn R. Cunningham‡‡‡, Hozefa A. Divan¶¶ and Raymond C. Rosen¶¶ for the RHYME Investigators

999 hypogonadal men who did and did not receive TTh. Over 36 months, positive biopsies were similar among men on TTh (37.5%) compared to those not on TTh (37.0%).

Terapia con Testosterone e sviluppo del carcinoma della prostata

VOLUME 35 · NUMBER 13 · MAY 1, 2017

JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

Testosterone Replacement Therapy and Risk of Favorable and Aggressive Prostate Cancer

Stacy Loeb, Yasin Folkvaljon, Jan-Erik Damber, Joseph Alukal, Mats Lambe, and Pär Stattin

(Nationwide, population-based registry data) No association between TTh and overall CaP risk (OR 1.03; 95% CI 0.90 to 1.17). Interestingly, men on TTh had a higher likelihood of favorable risk CaP (OR 1.35; 95% CI 1.16 to 1.56) and a lower risk of aggressive prostate cancer (OR 0.50; 95% CI 0.37 to 0.67) [53].

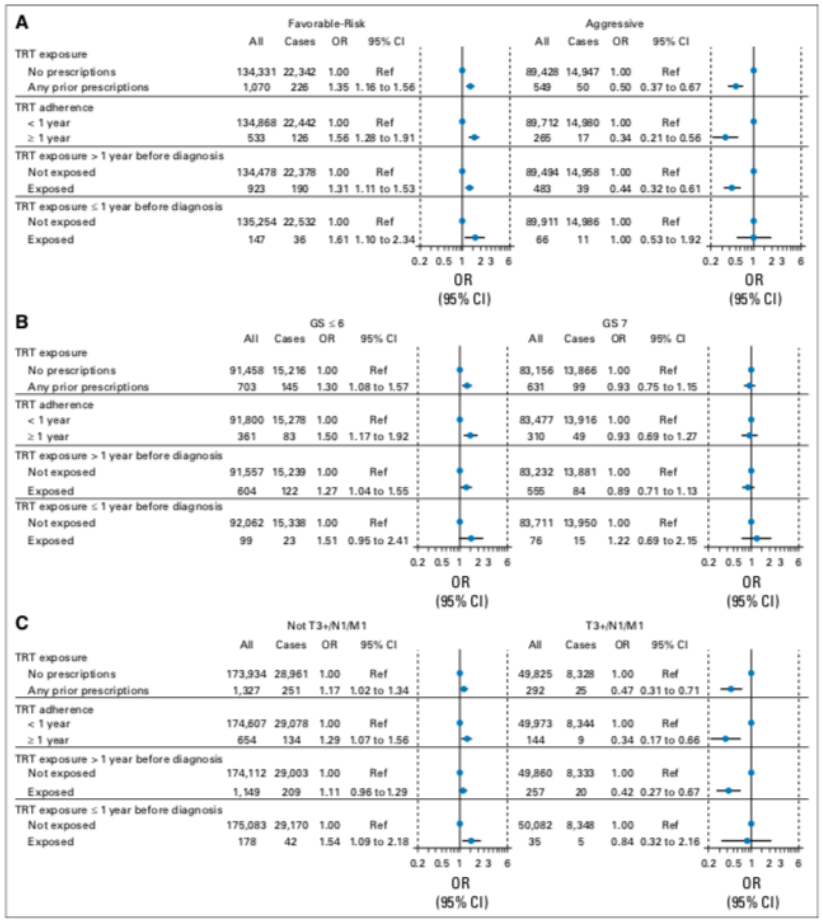


Fig 1. Odds ratios (ORs) with 95% CIs for prostate cancer according to exposure to testosterone replacement therapy (TRT) on the basis of three classifications of cancer aggressiveness: (A) favorable-risk versus aggressive cancer, (B) Gleason score (GS) ≤ 6 versus GS 7, and (C) not clinical T3+/N1/M1 versus T3+/N1/M1. Ref, reference.

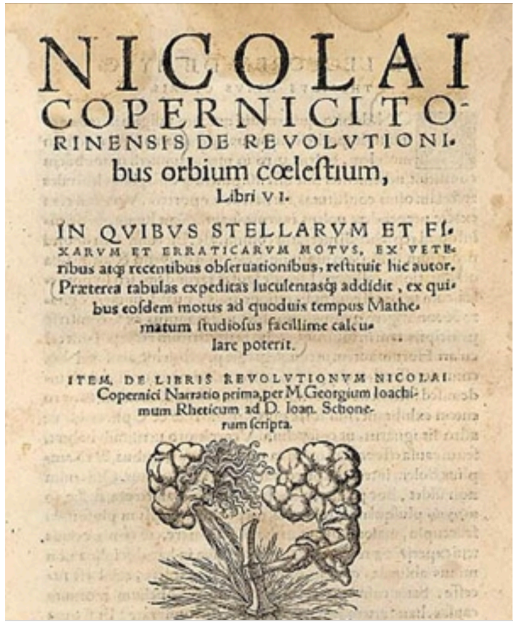
Testosterone nel paziente ipogonadico con carcinoma della prostata

Current Urology Reports (2018) 19: 67
https://doi.org/10.1007/s11934-018-0812-1

ANDROLOGY AND INFERTILITY (L LIPSHULTZ, SECTION EDITOR)

The Role of Testosterone Therapy in the Setting of Prostate Cancer

Katherine M. Rodriguez[1] · Alexander W. Pastuszak[2,3] · Mohit Khera[3]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Copernici Narratio prima, per M. Georgium Ioachi-
mum Rheticum ad D. Ioan. Schone-
rum ſcripta.

Table 1 Summary results of TTh in men with CaP, either treated with radical prostatectomy, radiation therapy, or on active surveillance

Authors	Year	CaP treatment	Findings	Reference
Kaufman et al.	2004	RP	- Seven men given TTh post-RP - No biochemical or clinical evidence of CaP recurrence	[54]
Khera M et al.	2009	RP	- 57 men post-RP on TTh - No biochemical recurrence or increase in PSA	[55]
Pastuszak et al.	2013	RP	- 103 men post-RP treated with TTh - 49 eugonadal men post-RP, no TTh - Statistically, but not clinically, significant increase in PSA in treatment groups - No increase in the control group	[8]
Sarosdy et al.	2007	Brachytherapy	- Retrospective analysis of 31 men treated with brachytherapy and TTH - Transient increases in PSA were observed in 1 patient	[56]
Morales et al.	2006	XRT	- Retrospective case series of 5 hypogonadal men post-external beam radiotherapy - Treated with TTh after PSA stabilized - One patient was observed to have an increase in PSA, but none had levels of > 1.5 ng/mL	[57]
Pastuszak et al.	2013	XRT/Brachytherapy	- Retrospective review of 13 hypogonadal men treated with brachytherapy or external beam radiotherapy - No significant increases in PSA or CaP recurrences	[58]
Balbontin et al.	2014	Brachytherapy	- 20 men treated with brachytherapy and subsequently with TTh. - Decrease in mean PSA from 0.7 ng/mL before TTh to 0.1 ng/mL at last follow-up ($p < 0.001$) - No CaP progression or recurrence	[59]
Pastusak et al.	2015	Brachytherapy	- Retrospective review of 98 after radiation - Increase in serum testosterone and no significant increase in mean PSA	[57]
Ory et al.	2016	AS	- 82 hypogonadal men with post-treatment CaP - Treated with TTh over a median of 41 months - Significant increase in PSA levels without Gleason score upstaging on prostate biopsies - No men went on to definitive treatment	[60]
Morgentaler et al.	2011	AS	- Retrospective case study of 13 men with CaP on AS - No changes in PSA or prostate volume were observed - Two men had Gleason score upgrading, one man had a biopsy with no upgrading, and one other man underwent RP that showed no CaP progression	[61]
Kacker et al.	2016	AS	- 96 men on AS alone compared to 28 hypogonadal men on AS and concurrent TTh - Both groups had comparable, biopsy-proven CaP progression rates	[62]

Il ruolo del testosterone nella patogenesi del tumore della prostata rimane controverso, ma alcune evidenze indicano che il basso testosterone sia correlato con l'incidenza, la peggiore prognosi e la peggiore sopravvivenza del tumore della prostata

TERAPIA?

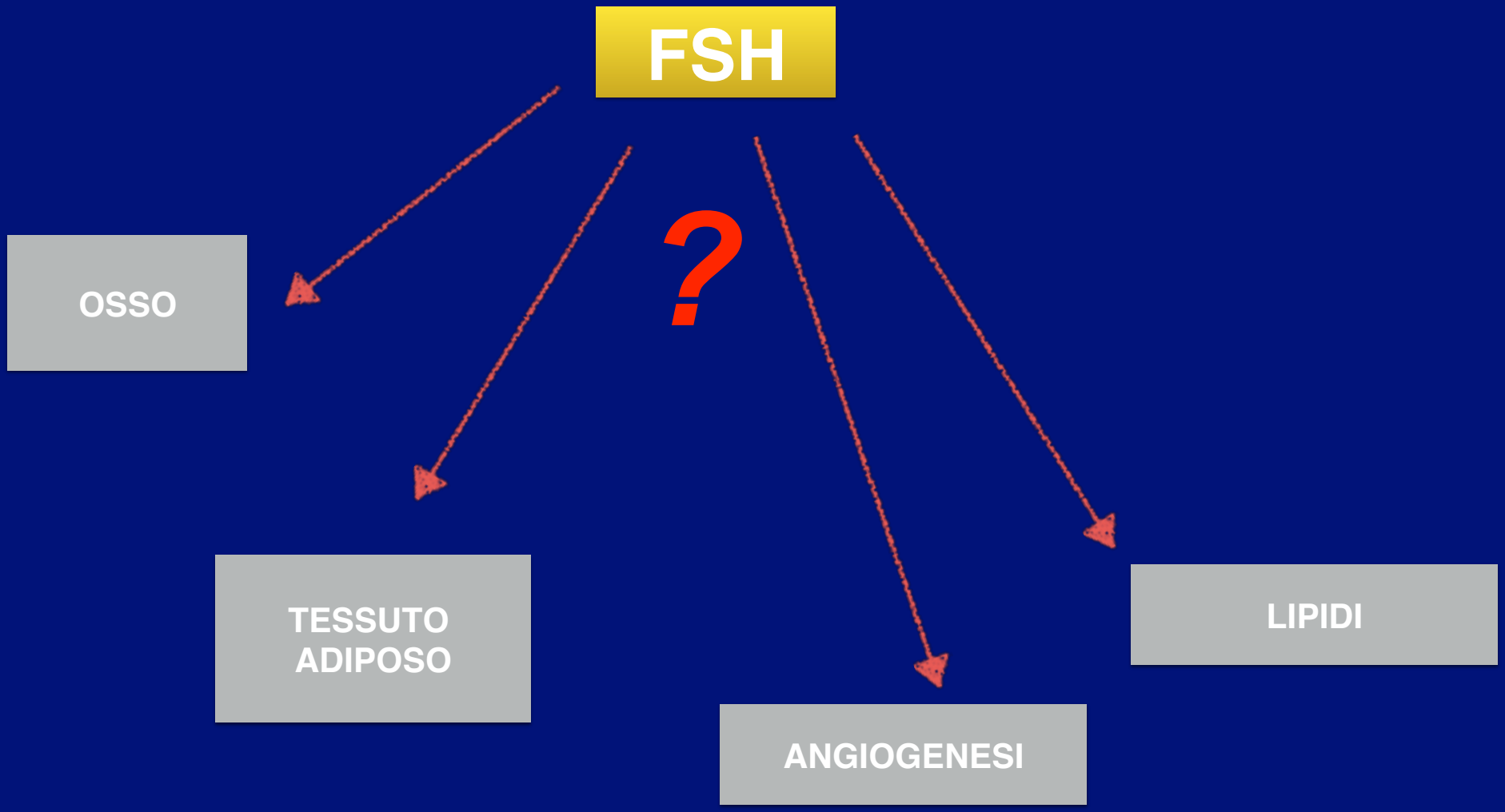
OFF LABEL!

Terapia con Testosterone e sviluppo del carcinoma della prostata

Although available studies do not support a link between TTh and prostate-specific antigen (PSA) levels or development/progression of CaP, careful monitoring of prostate size and serum PSA levels is recommended.

Effetti extra-gonadici dell'FSH

Effetti extra-gonadici dell'FSH



Effetti extra-gonadici dell'FSH

MINI-REVIEW

Extragonadal Actions of FSH: A Critical Need for Novel Genetic Models

T. Rajendra Kumar[1]

Table 1. A Summary of Extragonadal Expression of FSHRs and Putative Actions of FSH

Species	Extragonadal Tissue/ Cell Tissue Type	FSH Action Noted	Reference
Mouse	Bone (osteoclasts)	Bone resorption	Sun *et al.* (9)
Human	Umbilical vein endothelial cells, placenta	Angiogenesis	
Human and mouse	Female reproductive tract	Myometrial contractility	Stilley *et al.* (10, 11)
Human	Liver (hepatocytes)	Regulation of LDLR levels	Song *et al.* (25)
Chicken	Adipose	Stimulation of lipid biosynthesis	Cui *et al.* (35)
Human and mouse	Adipose	Beiging and mitochondrial biogenesis, activation of brown adipose tissue and enhances thermogenesis	Liu *et al.* (14, 36)

Effetti extra-gonadici dell'FSH - effetti sull'osso

Cell

FSH Directly Regulates Bone Mass

Li Sun,[1] Yuanzhen Peng,[1] Allison C. Sharrow,[2,3] Jameel Iqbal,[1] Zhiyuan Zhang,[1] Dionysios J. Papachristou,[2,3] Samir Zaidi,[1] Ling-Ling Zhu,[1] Beatrice B. Yaroslavskiy,[2,3] Hang Zhou,[1] Alberta Zallone,[4] M. Ram Sairam,[5] T. Rajendra Kumar,[6] Wei Bo,[7] Jonathan Braun,[7] Luis Cardoso-Landa,[1] Mitchell B. Schaffler,[1] Baljit S. Moonga,[1] Harry C. Blair,[2,3,*] and Mone Zaidi[1,*]

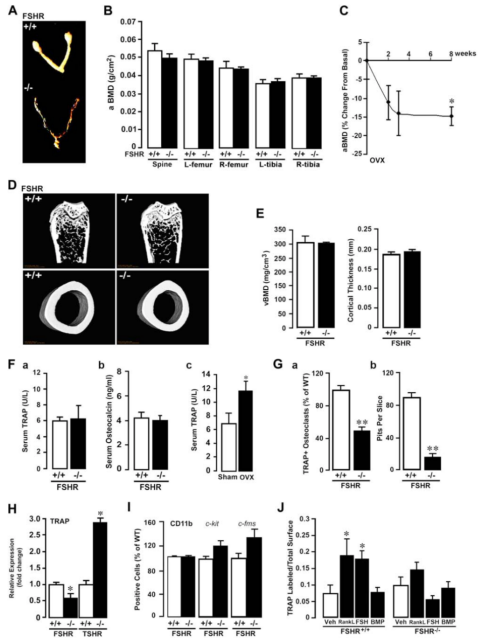


Figure 1. Conserved Bone Mass in Hypogonadal FSHR-Deficient Mice

(A) Hypogonadal FSHR$^{-/-}$ mice have hypoplastic uteri and atrophic ovaries.

(B) Areal bone mineral density (aBMD) in 4-month-old mice. Mean ± SEM (4–11 mice/group).

(C) Serial lumbar spine aBMDs following ovariectomy (OVX) of wild-type (wt) mice. Mean % change from basal (day 0) ± SEM (n = 4 mice); p = 0.021.

(D) Frontal (upper) and transverse (lower) μCT sections of distal femoral and middiaphyses.

(E) Volumetric BMD (vBMD) and cortical thickness at the distal and middiaphyses. Mean ± SEM (n = 3 mice/group).

(Fa–Fc) Serum TRAP (U/l, Fa and Fc) and osteocalcin (ng/ml, Fb) levels. Mean ± SEM (5–14 mice/group).

(Ga) TRAP-positive osteoclasts (100 ng/ml RANK-L). % of wt ± SEM, n = 12 wells/group, two experiments.

(Gb) Bone resorption by osteoclasts. Pits/slice ± SEM. n = 5 slices, 3 mice/group.

(H) Real-time PCR for *TRAP* mRNA in bone-marrow cultures (RANK-L, 60 ng/ml) for 5 days. Mean fold change from wt ± SEM; triplicate; pooled samples; normalized to *GAPDH*.

(I) FACS comparing cells for CD11b, c-Kit, and c-Fms. % of wt ± SEM, n = 3 mice/group.

(J) Effect of RANK-L (100 ng/ml), FSH (100 ng/ml), and BMP-2 (200 ng/ml) on TRAP-labeled surfaces/total surface in calvarial bones ex vivo (method modified from Novack et al., 2003). Multiple blinded measurements on three or four bones ± SEM. *p < 0.05, **p < 0.01.

In genetic models missing either the FSH ligand (Fshb null mice) or FSHRs (Fshr null mice) throughout the body from birth, the net bone density was shown to be maintained or increased in a Fshb/ Fshr gene dosage-dependent manner and independent of estrogen status.

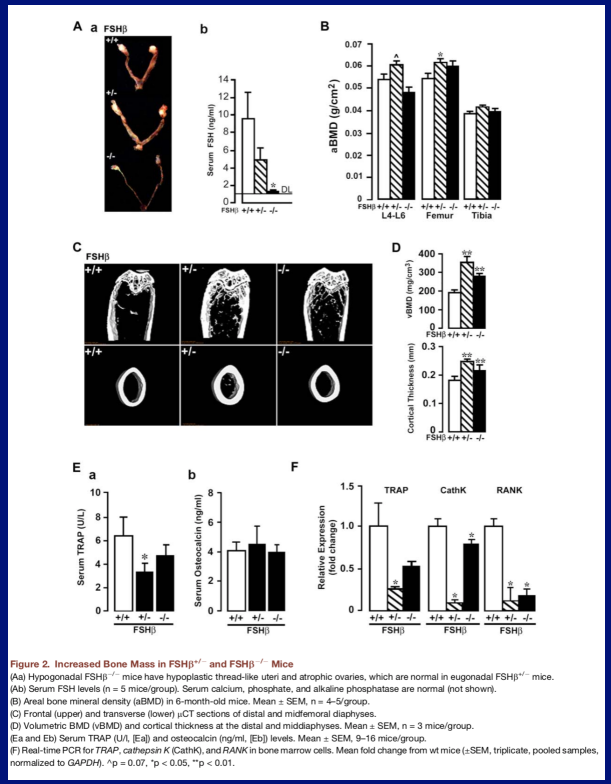


Figure 2. Increased Bone Mass in FSHβ$^{+/-}$ and FSHβ$^{-/-}$ Mice

(Aa) Hypogonadal FSHβ$^{-/-}$ mice have hypoplastic thread-like uteri and atrophic ovaries, which are normal in eugonadal FSHβ$^{+/-}$ mice.

(Ab) Serum FSH levels (n = 5 mice/group). Serum calcium, phosphate, and alkaline phosphatase are normal (not shown).

(B) Areal bone mineral density (aBMD) in 6-month-old mice. Mean ± SEM, n = 4–5/group.

(C) Frontal (upper) and transverse (lower) μCT sections of distal and midfemoral diaphyses.

(D) Volumetric BMD (vBMD) and cortical thickness at the distal and middiaphyses. Mean ± SEM, n = 3 mice/group.

(Ea and Eb) Serum TRAP (U/l, [Ea]) and osteocalcin (ng/ml, [Eb]) levels. Mean ± SEM, 9–16 mice/group.

(F) Real-time PCR for *TRAP*, *cathepsin K* (CathK), and *RANK* in bone marrow cells. Mean fold change from wt mice (±SEM, triplicate, pooled samples, normalized to *GAPDH*). ^p = 0.07, *p < 0.05, **p < 0.01.

Effetti extra-gonadici dell'FSH - effetti sull'osso

MINI-REVIEW

Extragonadal Actions of FSH: A Critical Need for Novel Genetic Models

T. Rajendra Kumar[1]

In the face of normal/declining estrogen levels, women experiencing perimenopausal transition maximally lose bone density, and this is strongly correlated to high levels of serum FSH.

Effetti extra-gonadici dell'FSH - effetti sull'osso

A large cohort of European women who were harboring polymorphisms in FSHR that lead to constitutively active FSHRs rapidly lost bone density

European Journal of Endocrinology (2010) **163** 165–172 ISSN 0804-4643

CLINICAL STUDY

FSHR gene polymorphisms influence bone mineral density and bone turnover in postmenopausal women

Domenico Rendina, Fernando Gianfrancesco[1], Gianpaolo De Filippo[2], Daniela Merlotti[3], Teresa Esposito[1], Alessandra Mingione[1], Ranuccio Nuti[3], Pasquale Strazzullo, Giuseppe Mossetti and Luigi Gennari[3]

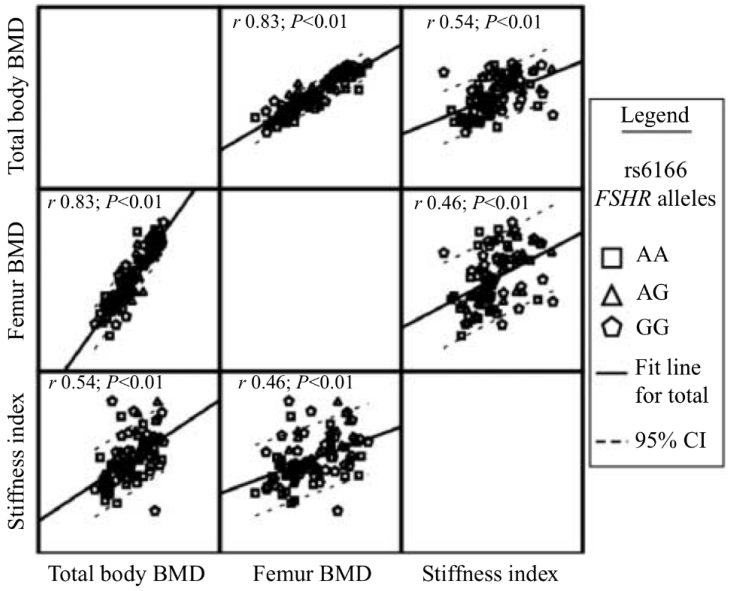
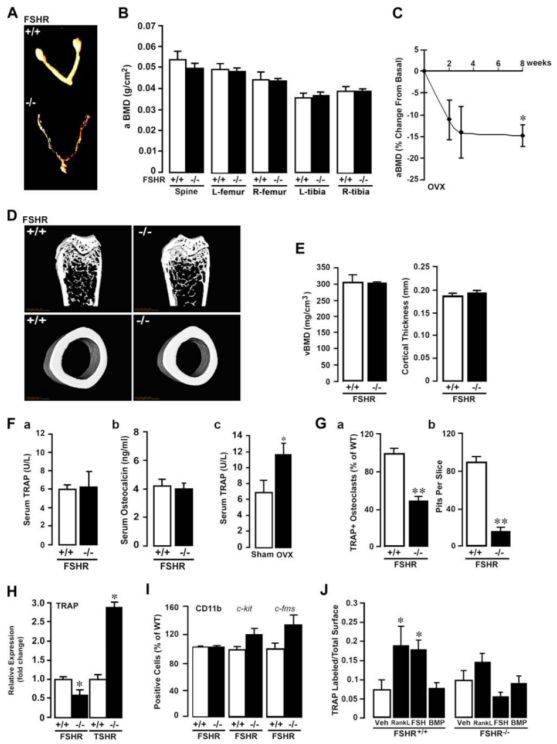


Figure 1 Correlation between total body BMD, femoral neck BMD, and stiffness index in the study population. BMD, bone mineral density; femur, femoral neck. Total body and femoral neck BMD, expressed as g/cm^2, were evaluated using dual-energy X-ray absorptiometry (DXA). Stiffness index (SI) was determined by quantitative ultrasound (QUS) and was calculated by a linear combination of speed of sound (SOS, m/s) and broadband ultrasound attenuation (BUA, dB/MHz) according to the formula (SI = (0.67 × BUA) + (0.28 × SOS) − 420). Postmenopausal women were classified according to single nucleotide polymorphism (SNP) rs6166, which occurs at codon 680 of the *FSHR* gene and causes an amino acid substitution Ser680Asn. Pearson's correlation coefficient was used to determine relationships between different parameters.

Effetti extra-gonadici dell'FSH - effetti sull'osso

Loss of bone density is prevented in ovariectomized female mice lacking FSHRs



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(I) FACS comparing cells for CD11b, c-Kit, and c-Fms. % of wt ± SEM, n = 3 mice/group.

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Effetti extra-gonadici dell'FSH - effetti sull'osso

Live imaging studies in which near-infrared fluorophore–coupled recombinant FSH ligand was injected into adult mice identified intense labeling of bones by FSH

Chemical Science

EDGE ARTICLE

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Cite this: *Chem. Sci.*, 2017, 8, 3703

Live imaging of follicle stimulating hormone receptors in gonads and bones using near infrared II fluorophore†

Yi Feng,‡§[a] Shoujun Zhu,‡[b] Alexander L. Antaris,‡[b] Hao Chen,[cd] Yuling Xiao,[c] Xiaowei Lu,[a] Linlin Jiang,[a] Shuo Diao,[b] Kuai Yu,[b] Yan Wang,[a] Sonia Herraiz,[a] Jingying Yue,[b] Xuechuan Hong,[c] Guosong Hong,[b] Zhen Cheng,*[d] Hongjie Dai*[b] and Aaron J. Hsueh*[a]

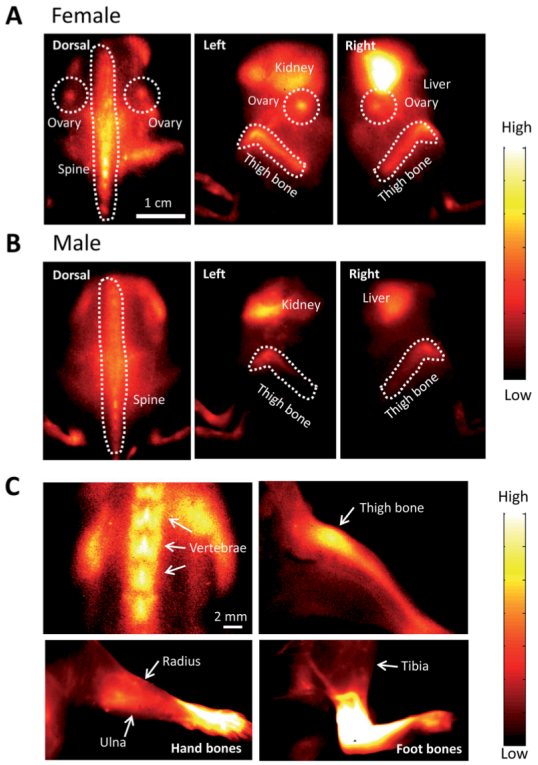


Fig. 5 NIR-II imaging of bones using follicle stimulating hormone-fluorophore CH1055 (FSH-CH) in adult female and male mice. FSH-CH (12.5 μg) was injected into the tail vein of mice before imaging bones at 2 h post-injection. (A) For female mice, a dorsal view shows strong NIR-II signals in the ovaries and spine. In the left side view, NIR-II signals were found in the ovary and thighbone together with nonspecific signals in the kidney, the site of FSH metabolism. In the right side view, NIR-II signals were found in the ovary and thighbone together with strong signals in the liver, the site of CH1055 metabolism. (B) For male mice, a dorsal view shows NIR-II signals in the spine. The left side view shows NIR-II signals in the thighbone together with non-specific signals in the kidney. The right side view shows NIR-II signals in the thighbone together with nonspecific signals in the liver. (C) High magnification of the vertebrae and thighbone of a female, together with the radius, ulna, and hand bones as well as the tibia and foot bones in a male.

Effetti extra-gonadici dell'FSH - effetti sull'osso

Presence of FSHRs exclusively on "bone-chewing" osteoclasts but not on bone-forming osteoblasts

FSH in vitro stimulated osteoclastogenesis and bone resorption

These effects on osteoclasts were specific to FSH was further illustrated by the absence of any effect by luteinizing hormone (LH), a hormone coexpressed with FSH in gonadotropes, and by gonadotropin-releasing hormone (GnRH)

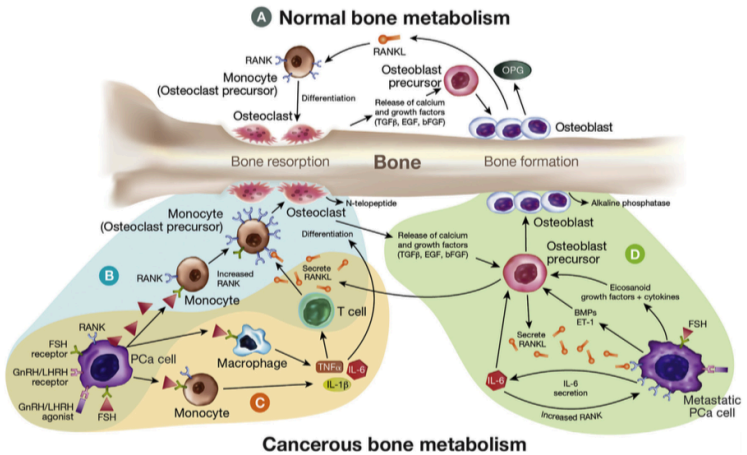


Fig. 2. (A) Normal bone metabolism involves a complex sequence of bone resorption (via osteoclasts) and bone formation (via osteoblasts). RANKL binds to RANK on osteoclast precursors, driving differentiation into osteoclasts. As osteoclasts resorb the bone matrix, a variety of growth factors and calcium is released, stimulating the differentiation of osteoblasts precursors into osteoblasts. OPG is a soluble inhibitor of RANKL that provides negative feedback on the process. (B) Prostate cancer cells can release FSH, which increases RANK expression on osteoclast precursors, increasing the probability that RANKL (released by osteoblasts and T cells) will bind to RANK and drive differentiation to osteoclasts. (C) FSH induces monocytes and macrophages to release TNFα, which stimulates T cells to secrete RANKL and drive differentiation of osteoclast precursors. FSH also stimulates monocytes to release IL-1β and IL-6, which further increase osteoclast differentiation and bone resorption. (D) RANKL in the bone microenvironment stimulates metastatic prostate cancer cells to release IL-6, which increases the expression of RANK on prostate cancer cells, facilitating additional RANKL-mediated release of IL-6, and initiating a positive feed-forward cycle. IL-6 also stimulates further release of RANKL from osteoblasts and osteoblast precursors. Factors released from the bone matrix after resorption by osteoclasts and by metastatic prostate cancer cells in the bone stimulate osteoblast differentiation and activity. These factors (especially TGFβ) also further stimulate cancer growth, leading to "vicious cycle." bFGF = basic fibroblast growth factor; BMP = bone morphogenic proteins; EGF = epidermal growth factor; ET-1 = endothelin-1; FSH (R) = follicle-stimulating hormone (receptor); GnRH/LHRH = gonadotropin-releasing hormone/luteinizing hormone–releasing hormone; OPG = osteoprotegerin; RANK (L) = receptor activator of NFκB (ligand); TGFβ = transforming growth factor beta; TNF-α = tumor necrosis factor alpha.

UROLOGIC ONCOLOGY
Review article
The potential role of follicle-stimulating hormone in the cardiovascular, metabolic, skeletal, and cognitive effects associated with androgen deprivation therapy
E. David Crawford, M.D.[a,*], Andrew V. Schally, Ph.D., M.D.h. (Mobil), D.Sc. (h)[b,c,d], Jonathan H. Pinthus, M.D., Ph.D.[e], Norman L. Block, M.D.[f,g], Yvonne G. Fizazi, M.D., Ph.D.[h], Max B. Gorin, M.D.[i], Robert F. Ittel, M.D.[j], Yvonne E. Kranz, M.B.B.Ch., F.R.C.S.I., F.A.C.S.[k], Neil D. Shore, M.D., F.A.C.S., C.P.I. David N. Slobod, M.S., Ph.D.[l], Thomas J.R. Beveridge, M.Sc., Ph.D.[l], Dorian C. Marshall, B.N., M.S., Ph.D.[l]

Effetti extra-gonadici dell'FSH - effetti sull'osso di anticorpo bloccante mediati da TNF alfa

FSH action in the osteoclast linage cells leads to the production of cytokines, including tumor necrosis factor alpha (TNF-a), the typical inflammatory cytokine. Interestingly, FSHb null mice have lower TNF-a levels, and mice lacking TNF-a are indeed resistant to hypogonadal bone loss in the presence of high FSH levels compared to controls. Thus, it was suggested that TNF-a is critical to the effect of FSH on bone mass.

Follicle-stimulating hormone stimulates TNF production from immune cells to enhance osteoblast and osteoclast formation

Jameel Iqbal*, Li Sun*, T. Rajendra Kumar†, Harry C. Blair‡, and Mone Zaidi*§

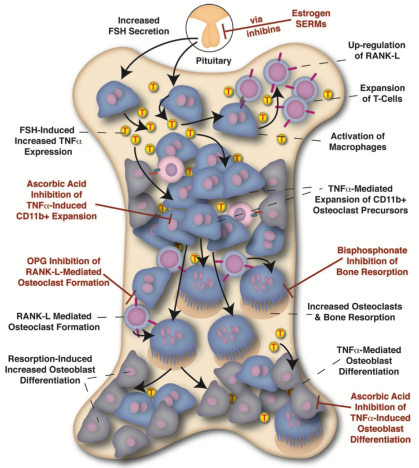
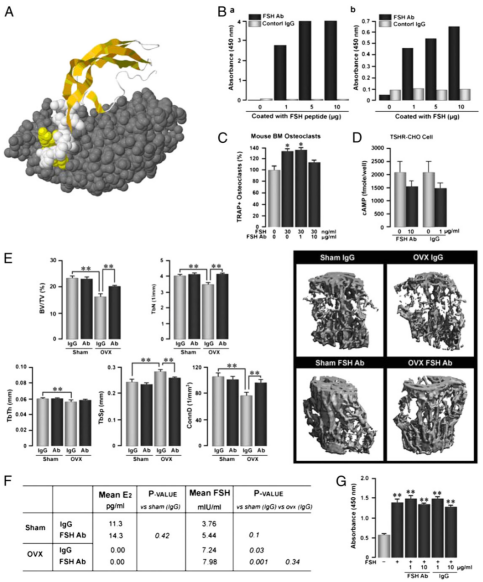


Fig. 4. Integrated hypothesis for hypogonadal bone loss. Ovarian dysfunction and the loss of estrogen lead to decreased inhibin levels and dramatic increases in FSH levels. FSH, in turn, directly stimulates osteoclast differentiation and TNFα production from bone marrow macrophages/granulocytes. TNFα (shown as T) acts to increase M-CSF levels and/or M-CSF receptor expression, resulting in an expansion of the number of osteoclast precursors. Additionally, TNFα may prime macrophages to induce the proliferation of activated T lymphocytes, which highly express RANK-L and further contribute to TNFα production. The overabundance of osteoclast precursors, coupled with the osteoclastic differentiation agents FSH and RANK-L, which is expressed on T lymphocytes and stromal cells, likely compose the proosteoclastic component of high-turnover bone loss. TNFα-induced increases in the number of osteoblasts, as well as resorption-induced osteoblast formation, likely compose the proosteoblastic component of high-turnover bone loss. TNFα action can be blocked by treatment with etanercept or analogs, or, as we have found in this report, through supplementation with ascorbic acid (vitamin C). The proosteoclastogenic actions of RANK-L can be blocked by RANK-Fc or OPG. The resorptive function of osteoclasts can be blocked by bisphosphonates, which are taken up by resorbing osteoclasts and modulate their sensitivity to apoptotic stimuli. Estrogen replacement therapy or selective estrogen receptor modulator (SERM) therapy, per our hypothesis, may decrease FSH levels to reduce TNFα expression.

Effetti extra-gonadici dell'FSH - effetti sull'osso di anticorpo bloccante FSH

When intraperitoneally injected, the blocking antibody significantly reduced ovariectomy-induced bone loss in mice.

Surprisingly, the blocking FSHb antibody stimulated bone formation, most likely via blocking FSHR-mediated effects on mesenchymal stem cells.



		Mean E_2 pg/ml	P.VALUE vs sham (IgG)	Mean FSH mIU/ml	P.VALUE vs sham (IgG) vs ovx (IgG)	
Sham	IgG	11.3		3.76		
	FSH Ab	14.3	0.42	5.44	0.1	
OVX	IgG	0.00		7.24	0.03	
	FSH Ab	0.00		7.98	0.001	0.34

Fig. 1. Antibody directed to the receptor-binding domain of the β-subunit of FSH (FSH Ab) prevents ovariectomy-induced bone loss. (*A*) FSH antibody blocks FSH binding to FSHR by steric hindrance. The crystal structure of the β-subunit of FSH (36) (ribbon cartoon highlighted with space-filled atoms in yellow and white) and the truncated FSHR ectodomain (space-filled atoms in gray) complex is shown (Protein Data Bank ID code: 1XWD). FSHβ residues buried at the receptor–ligand surface interface, underlined in this peptide sequence LVYKDPARPKIQK from which the FSH antibody is generated, are shown as yellow space-filled atoms. FSHβ residues, which are not buried, are shown as white space-filled atoms. Binding of the FSH antibody to the FSHβ subunit disrupts its interaction with the FSHR. For illustration purposes, the FSHα subunit is not shown in the complex. (*B*) Enzyme-linked immunoabsorbent assay (ELISA) demonstrating binding of the anti-FSH antibody (FSH Ab) or control IgG to either the FSH peptide fragment (*a*) or full-length FSH (*b*) (concentrations of plated peptide are shown). (*C*) Tartrate-resistant acid phosphatase-positive (TRAP$^+$) osteoclasts formed in murine bone marrow cell cultures treated with FSH (30 ng/mL) with or without FSH Ab (1 or 10 μg/mL). Statistics: Student *t* test; comparisons against zero-dose control; $^*P \leq 0.05$; $n = 8$ wells per group. (*D*) cAMP responses in TSH receptor (TSHR) overexpressing CHO cells induced by TSH either without incubation (light bars) or following incubation (dark bars) with FSH Ab (10 μg/mL) or control goat IgG (1 μg/mL). Statistics: mean ± SEM; Student *t* test; comparisons against TSH alone. Overall, the data show that FSH Ab specifically detects FSH and not TSH and inhibits the osteoclastogenesis induced by FSH. (*E*) Effect of FSH Ab injections (100 μg/d), beginning the day of ovariectomy (OVX), on bone loss, measured by micro-CT, and shown as bone volume/total volume (BV/TV), trabecular number (TbN), trabecular thickness (TbTh, trabecular spacing (TbS), and connectivity density (ConnD). Statistics: Student *t* test with Bonferroni's correction; comparisons as shown, $^*P \leq 0.05$; $^{**}P \leq 0.01$; $n = 8$ mice per group. (*F*) Mean plasma estradiol (E_2) and FSH levels in sham-operated and OVX mice treated with IgG or FSH Ab (100 μg/d). Statistics: Student *t* test; *P* values as shown; $n = 8$ mice per group. (*G*) Effect of preincubating FSH Ab or IgG (concentrations as noted) with FSH (1 μg per well) on the ability of the ELISA to detect FSH (absorbance at 450 nm). Notably, binding of FSH Ab to FSH does not reduce the levels of FSH detectable by the ELISA antibody. Statistics: Student *t* test; comparisons against zero-dose control; $^{**}P \leq 0.01$; in duplicate.

Blocking antibody to the β-subunit of FSH prevents bone loss by inhibiting bone resorption and stimulating bone synthesis

Ling-Ling Zhu[a,b], Harry Blair[c,d], Jay Cao[e], Tony Yuen[a], Rauf Latif[a], Lida Guo[c], Irina L. Tourkova[c], Jianhua Li[a], Terry F. Davies[a], Li Sun[a], Zhuan Bian[b], Clifford Rosen[f], Alberta Zallone[g], Maria I. New[a,1], and Mone Zaidi[a,1]

Effetti extra-gonadici dell'FSH - effetti sull'osso di anticorpo bloccante FSH

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Blocking FSH action attenuates osteoclastogenesis

Ling-Ling Zhu [a,b], Irina Tourkova [c,d], Tony Yuen [b], Lisa J. Robinson [c,d], Zhuan Bian [a], Mone Zaidi [b,*,1], Harry C. Blair [c,d,e,*,1]

A

Anti-FSH	Monoclonal Anti-FSHβ			Polyclonal Anti-mouse FSHβ		
	0	0	1 μg/ml	0	0	0.01 mg/ml
FSH	0	30	30 ng/ml	0	30	30 ng/ml
OCs	59 ±2.65	68 ±3.21	53 ±2.38	58 ±3.58	68 ±2.96	56 ±2.12
p vs Control		*0.036*	*0.061*		*0.025*	*0.351*
30 ng/ml FSH			*0.001*			*0.003*

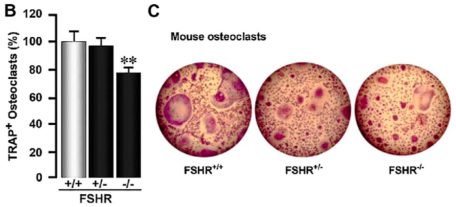

Fig. 1. FSH increases osteoclastic differentiation from mouse marrow cells, but the effect is abrogated by neutralizing antibodies. (A) Blocking antibodies for FSH reverse the effect of FSH on osteoclast formation. Bone marrow cells from 6 month old mice were isolated and osteoclast differentiation was induced with murine RANKL and murine CSF-1 [1]. This increased osteoclast formation by ~20%; duplicate experiments are shown. In the first experiment monoclonal anti-FSHβ was added in excess and this eliminated eliminating the effect of FSH ($p = 0.001$). In the second experiment polyclonal anti-FSHβ also returned osteoclast formation to background ($p = 0.003$). (B) The effect of FSHR deletion on osteoclast formation is shown. Multinucleated TRAP-expressing osteoclasts 5-days after RANK-L treatment were attenuated in FSHR$^{-/-}$ cultures compared with FSHR$^{+/+}$ or wild type ($p < 0.001$ FSHR$^{-/-}$ relative to WT littermates). The size of the effect was similar to that seen when FSH is added during osteoclast formation in wild type cells (A). (C) Photomicrographs of multinucleated TRAP-expressing cells in wild type, FSHR$^{+/-}$, and FSHR$^{-/-}$ marrow cell cultures with 30 ng/ml of FSH during differentiation in RANKL and CSF-1. The knockout cells produce fewer multinucleated cells.

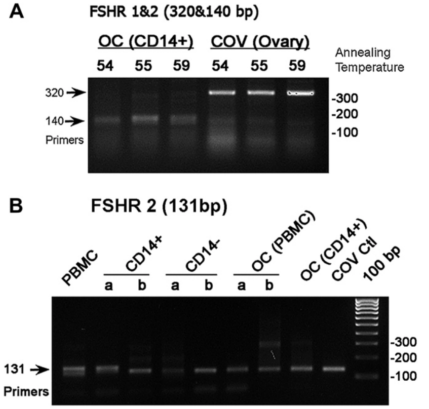

Fig. 2. An alternatively spliced FSH receptor transcript is expressed in human osteoclasts, CD14+ monocytes, and CD14-depleted monocytic cells. (A) FSHR isoform 1 is expressed in the ovary, but a truncated form is the main form found in monocytes and osteoclasts. Primer set 1 (Methods), amplifying across exon 9, shows the full length FSHR fragment from distal exon 8 to early exon 10, and the smaller isoform missing exon 9. The smaller, type 2 isoform, 140 bp, is barely visible in ovary, but is the major product in osteoclasts made from CD14 cells with 14 day incubation in RANKL and CSF-1. Exon 9 is a short extracellular exon just distal to the FSH-binding sequence and proximal to the invariant transmembrane signaling region, exon 10. Results from three reactions in a temperature gradient PCR are shown. Further reactions were annealed at 54 °C. (B) FSHR isoform 2 with exon 9 omitted. Primer set 2, the forward primer of which extends across the exon 8–10 boundary, was used, and the products of 30 cycles of amplification were then re-amplified with an internal nested primer set (131 bp) for a further 20 cycles. Transcript of this isoform was seen in fractions of peripheral blood mononuclear cells (unselected, CD14-selected, CD14-depleted, and osteoclasts from CD14+ cells), and ovarian control (COV) cells. Presence of the smaller isoform, at low levels, in ovarian cells was previously described (see text).

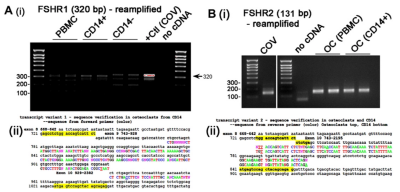

Fig. 3. Sequence confirmation of an alternatively spliced FSH receptor transcript. (A) (i) Full length FSHR transcript noted in osteoclasts. Bands at 320 bp from agarose gels (A) were excised, re-amplified 10 cycles, and (ii) direct sequencing of the PCR products was performed. Sequence of the FSHR from osteoclasts using the forward primer, extending across the exon 9–10 boundary, is shown in color below the reference genomic sequence. The ovarian product also matched the reference sequence (not shown). The osteoclast sequence had several unresolved bases (pink) and two mismatches (underlined), which are probably misreads due to low level signal, but might also be amplification errors. Bases in yellow are primer pair 1. (B) The FSHR isoform 2, missing exon 9, is expressed in osteoclasts and CD14 cells. Bands at 140 bp from agarose gels (i) were excised, re-amplified using primer set 2 for 10 cycles, and direct sequencing of the products was performed (ii). Sequence from the reverse primer, extending across the exon 8–10 boundary, is shown in color below the reference genomic sequence, for both osteoclasts (top color sequence) and CD14 cell (lower color sequence) amplicons. Bases in yellow are primer pair 2. The reference sequence was also obtained from control ovarian cells, and in the PCR product amplified from CD14 depleted cells (neither shown). As in (A), unresolved bases are shown in pink and misreads are underlined. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Effetti extra-gonadici dell'FSH - effetti sul tessuto adiposo

In addition to bone loss, the late perimenopausal transition is associated with enhanced visceral adiposity and is coincident with disrupted energy balance and reduced physical activity.

At this and later stages of menopause, the effects of loss of estrogen action on energy balance are less understood.

Effetti extra-gonadici dell'FSH - effetti sul tessuto adiposo

When injected into wild-type mice on a high-fat diet, the FSH polyclonal antibody caused a reduction in both fat mass measured by quantitative nuclear magnetic resonance analyses and total, visceral, subcutaneous fat volume as measured by micro-computed tomography.

Moreover, the antibody reduced adiposity in ovariectomized mice. Consistent with these effects of FSH signaling on adipose tissue, immunostaining with FSHR antibodies revealed intense FSHR staining in white (inguinal and visceral) and brown adipose tissues. Strikingly, the blocking antibody activated the mitochondrial uncoupling protein 1, enhanced mitochondrial biogenesis, and triggered white-to-brown adipose tissue conversion.

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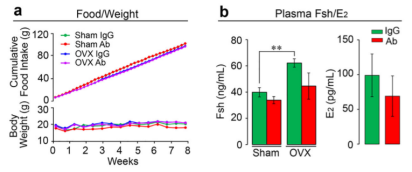
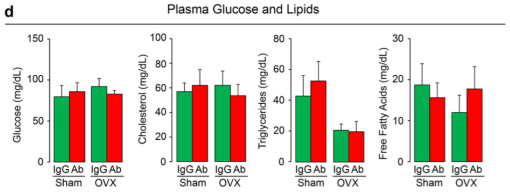
Blocking FSH Induces Thermogenic Adipose Tissue and Reduces Body Fat

Peng Liu[1,*], Yaoting Ji[1,2,*], Tony Yuen[1], Elizabeth Rendina-Ruedy[3], Victoria E. DeMambro[3], Samarth Dhawan[1], Wahid Abu-Amer[1], Sudeh Izadmehr[1], Bin Zhou[4], Andrew Shin[1], Rauf Latif[1], Priyanthan Thangeswaran[1], Animesh Gupta[1], Jianhua Li[1], Valeria Shnayder[1], Samuel T. Robinson[4], Yue Eric Yu[4], Xingjian Zhang[4], Feiran Yang[4], Ping Lu[1], Yu Zhou[1], Ling-Ling Zhu[1], Douglas J. Oberlin[1], Terry F. Davies[1], Michaela R. Reagan[3], Aaron Brown[3], T. Rajendra Kumar[5], Solomon Epstein[1], Jameel Iqbal[6], Maria I. New[1], Henrik Molina[7], Jan B. van Klinken[8], Edward X. Guo[4], Christoph Buettner[1], Shozeb Haider[9], Zhuan Bian[2], Li Sun[1,#], Clifford J. Rosen[3,#], and Mone Zaidi[1,#]



c Indirect Calorimetry

	Sham			OVX		
	IgG	Ab	*Pvalue*	IgG	Ab	*Pvalue*
Thermogenesis Parameters						
RQ (%)	0.77±0.003	0.72±0.01	*0.001*	0.77±0.01	0.72±0.01	*0.04*
R-EE (Kcal/30min)	0.41±0.02	0.45±0.02	*NS*	0.37±0.02	0.40±0.01	*NS*
A-EE (Kcal/15min)	0.59±0.04	0.68±0.02	*NS*	0.53±0.02	0.59±0.01	*0.04*
Activity Parameters						
Wheel Meters (m,x1000)	5.73±1.62	8.12±0.39	*NS*	1.84±0.47	2.80±0.74	*NS*
Wheel Speed (m/s)	0.23±0.03	0.25±0.01	*NS*	0.19±0.01	0.19±0.01	*NS*
Ped Meters (m)	124±12.0	150±18.4	*NS*	151±7.59	115±9.71	*0.03*
Ped Speed (cm/s)	1.41±0.08	1.54±0.07	*NS*	1.46±0.06	1.33±0.03	*NS*
Food Intake						
Food (g)	3.21±0.31	3.41±0.55	*NS*	3.57±0.64	2.92±0.11	*NS*



Extended Data Figure 5. Fsh Ab Effects in Ovariectomized Mice

Ovariectomized or sham-operated mice on normal chow injected with Fsh antibody (Ab) or goat IgG (200 or 400 μg/mouse/day to sham-operated and ovariectomized mice, respectively) (see Methods and Fig. 2). Shown are food intake and body weight (**a**) (n=5/group); plasma Fsh and estrogen (E_2) levels (plasma E_2 mostly undetectable after ovariectomy) (n=4 or 5/group) (**b**). Indirect calorimetry (metabolic cages) showing 24-hour respiratory quotient (RQ), resting EE (R-EE), active EE (A-EE), running distance (Wheel Meters), running speed (Wheel Speed), walking distance (Ped Meters), walking speed (Ped Speed) and food intake (n=4/group) (**c**). Absent effects of Fsh Ab or IgG on plasma glucose,

Effetti extra-gonadici dell'FSH - prospettive

Thus, the FSHb anti-peptide antibody appears to be a potential dual-purpose reagent that could have promising clinical applications in the future in treating both osteoporosis and obesity in postmenopausal women.

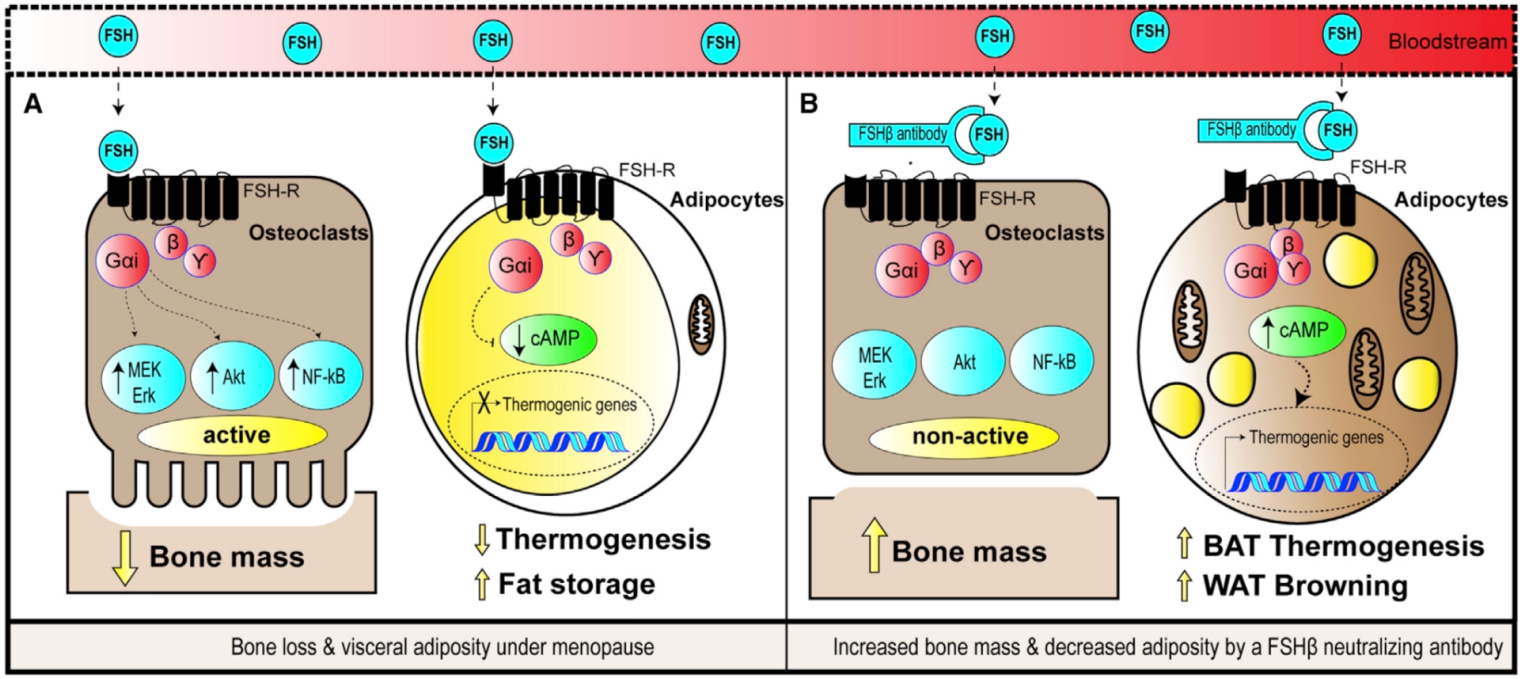


Figure 1. The Role of Follicle-Stimulating Hormone in Osteoclasts and Adipocytes

(A and B) Follicle-stimulating hormone (FSH) activates FSH receptor (FSH-R) that is coupled to the inhibitory G protein (Gi). (A) In menopause, increased FSH levels in the circulation trigger several signaling pathways in osteoclasts, such as MEK/Erk, Akt, and NF-κB, leading to the activation of osteoclastogenesis and bone reabsorption. In adipocytes, activation of the Gi protein via FSH-R decreases cAMP levels and thermogenic gene expression. (B) When the FSH signaling is blocked by a neutralizing antibody, osteoclast activity and subsequent bone reabsorption are inhibited. In adipocytes, the FSH antibody also activates brown/beige fat thermogenesis through promoting UCP1 expression.

Burning Fat and Building Bone by FSH Blockade

Carlos Henrique Sponton[1,2] and Shingo Kajimura[1,*]
[1]Diabetes Center and Department of Cell and Tissue Biology, University of California, San Francisco, San Francisco, CA, USA
[2]Obesity and Comorbidities Research Center—OCRC, University of Campinas (UNICAMP), Campinas, Sao Paulo, Brazil
*Correspondence: skajimura@diabetes.ucsf.edu
http://dx.doi.org/10.1016/j.cmet.2017.07.018

Effetti extra-gonadici dell'FSH - effetti sul colesterolo

Correlation between elevated FSH and serum lipid levels in 400 Chinese post-menopausal women.
At least twofold-elevated FSH levels correlated to higher serum total cholesterol and low-density lipoprotein cholesterol (LDL-C) levels.

The proposed mechanism involves FSH interaction with its receptors in hepatocytes to reduce LDLR levels, which subsequently blocks the endocytosis of LDL-C and elevates circulating LDL-C levels.

ORIGINAL ARTICLE

Follicle-Stimulating Hormone Induces Postmenopausal Dyslipidemia Through Inhibiting Hepatic Cholesterol Metabolism

Yang Song, En-Sheng Wang, Li-Li Xing, Shuai Shi, Fan Qu, Dan Zhang, Jing-Yi Li, Jing Shu, Ye Meng, Jian-Zhong Sheng, Jian-Hong Zhou, and He-Feng Huang

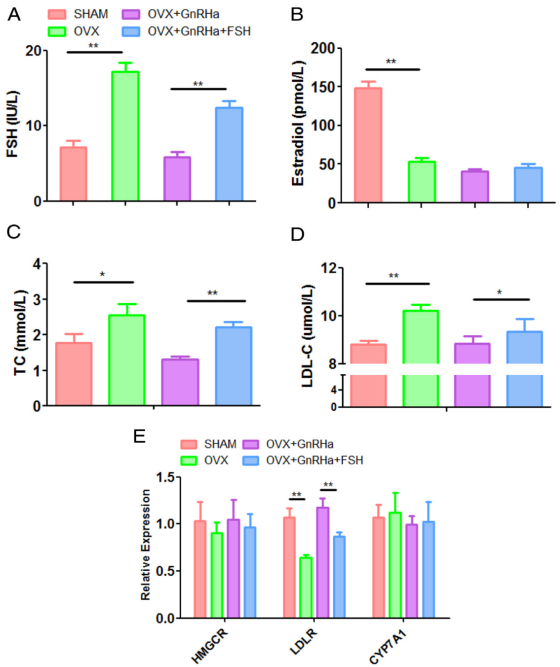


Figure 2. Lipid profile changes induced by high levels of FSH in mice. (A) FSH, (B) estradiol, (C) TC, and (D) LDL-C levels in mice treated with sham ovariectomy (SHAM), ovariectomy (OVX), OVX + GnRHa, or OVX + GnRHa + FSH. (E) Relative expression of liver gene transcript levels for HMGCR, LDLR, and CYP7A1 under the same treatment conditions as panels A–D. *, $P < .05$; **, $P < .01$.

Effetti extra-gonadici dell'FSH - angiogenesi tumorale

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Expression of Follicle-Stimulating Hormone Receptor in Tumor Blood Vessels

Aurelian Radu, Ph.D., Christophe Pichon, Ph.D., Philippe Camparo, M.D., Martine Antoine, M.D., Yves Allory, M.D., Anne Couvelard, M.D., Gaëlle Fromont, M.D., Mai Thu Vu Hai, Ph.D., and Nicolae Ghinea, Ph.D.

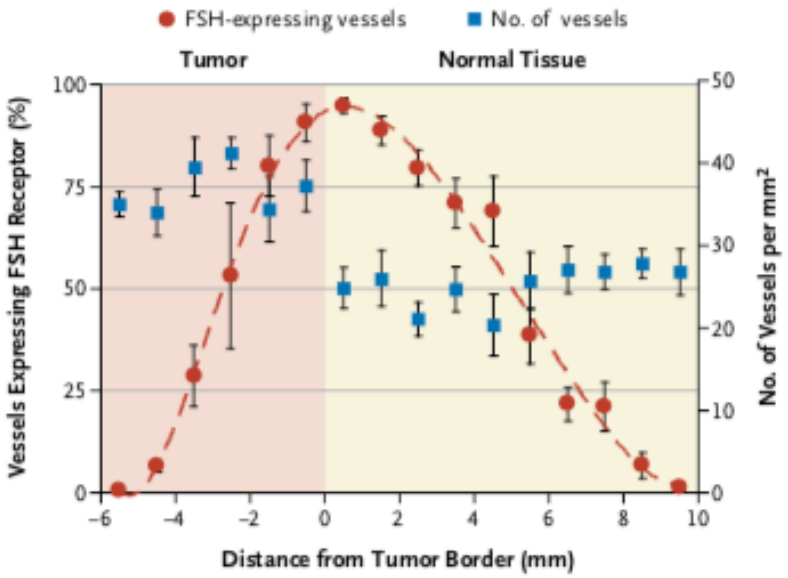


Figure 4. FSH-Receptor Expression According to Vessel Location.

The blood vessels were visualized with the use of anti–von Willebrand factor antibodies followed by Alexa-488 dye secondary antibodies, and FSH-receptor–stained vessels were visualized by the FSHR323 antibody followed by Alexa-555 dye–labeled secondary antibodies. The vessels were counted on 148 microscopical digital images of tumors obtained from five patients. Zero indicates the border of the tumor, the negative numbers indicate the interior of the tumor, and the positive numbers indicate the exterior of the tumor. The red circles and dashed line represent the percentage of FSH-receptor–expressing vessels. The blue squares indicate the total number of vessels per square millimeter; the mean number was higher in the interior of the tumor than in the exterior (37±2 vs. 25±1 vessels per square millimeter, $P<0.001$ with the use of a two-tailed t-test). I bars denote standard errors.

Effetti extra-gonadici dell'FSH - angiogenesi tumorale

MINI-REVIEW

Vascular Endothelial FSH Receptor, a Target of Interest for Cancer Therapy

Nicolae Ghinea[1]

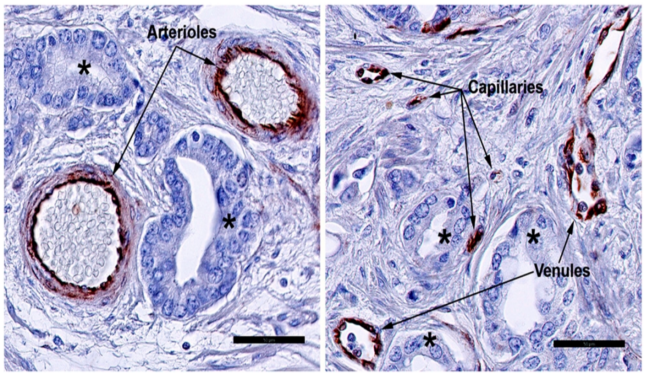


Figure 1. Expression of hFSHR by vascular endothelial cells in the tumor microenvironment. IHC analysis was performed on paraffin-embedded sections of human prostate cancer tissues with the use of the anti-FSHR monoclonal antibody 323, followed by a secondary peroxidase-coupled antibody visualized with the use of the red-brown peroxidase-reaction product. Sections were also stained with hematoxylin. The FSHR-positive blood microvessels are arranged in a hierarchical pattern: arterioles-capillaries-venules. Similar results were obtained with tissues obtained from other types of human cancer. No FSHR signal was visible in the tumor cells (asterisks). The scale bar represents 50 μm in both panels.

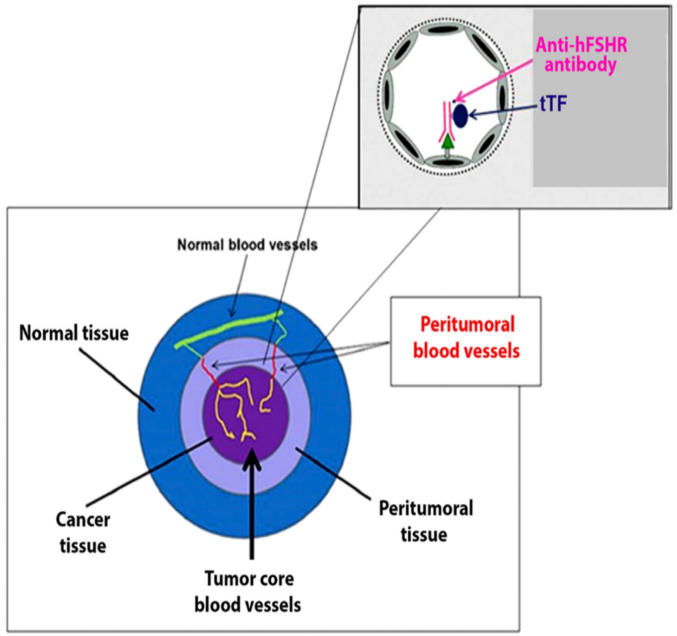


Figure 2. Infarction of peritumoral blood vessels rather than blocking the intratumor vasculature. Peritumoral blood vessels (in red) make connections between the intratumor vessels (in yellow) and the general blood circulation (in green) of patients. Using tTF coupled to anti-hFSHR antibodies, a selective concentration of tTF on luminal aspect of FSHR-positive endothelia should initiate the blood coagulation cascade, the formation of a blood clot, and thus the occlusion of peritumoral blood vessels. As previously indicated (69), a single blood clot should be enough for the congestion of a single vessel and subsequent death of thousands of cancer cells, including the actively proliferating cancer cells at the periphery of the tumor. tTF, truncated form of tissue factor.

Effetti extra-gonadici dell'FSH - ruolo nella deprivazione androgenica?

ELSEVIER

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Urologic Oncology: Seminars and Original Investigations 35 (2017) 183–191

UROLOGIC ONCOLOGY

Review article

The potential role of follicle-stimulating hormone in the cardiovascular, metabolic, skeletal, and cognitive effects associated with androgen deprivation therapy

E. David Crawford, M.D.[a,*], Andrew V. Schally, Ph.D., M.Dhc. (Multi), D.Sc., hc[b,c,d], Jehonathan H. Pinthus, M.D., Ph.D.[e], Norman L. Block, M.D.[b,c,d], Ferenc G. Rick, M.D., Ph.D.[b,f], Marc B. Garnick, M.D.[g], Robert H. Eckel, M.D.[h], Thomas E. Keane, M.B.B.Ch., F.R.C.S.I., F.A.C.S.[i], Neal D. Shore, M.D., F.A.C.S., C.P.I.[j], David N. Dahdal, M.S., Ph.D.[k], Thomas J.R. Beveridge, M.Sc., Ph.D.[k], Dennis C. Marshall, R.N., M.S., Ph.D.[k]

Representative articles summarizing the unwanted effects associated with androgen deprivation therapy and their relationship to follicle-stimulating hormone

Effect of ADT	Potential role of FSH	References
Cardiovascular morbidity and mortality	Dyslipidemia, plaque formation, and disruption	[25,49–51,57]
Metabolic syndrome	Adipocyte rearrangement, metabolic derangement, and insulin resistance	[28,29,48,52,54]
Bone loss, fracture, and metastasis	Increased osteoclast expression through RANK- and TNF-α-mediated pathways	[26,70,71,78,81]
Cognitive impairment	Associated with decreased testosterone and increased FSH and LH levels	[84,85,87,89,91]

Effetti extra-gonadici dell'FSH - dati in vivo?

ORIGINAL RESEARCH

American Heart Association | American Stroke Association

Follicle-Stimulating Hormone, Its Association with Cardiometabolic Risk Factors, and 10-Year Risk of Cardiovascular Disease in Postmenopausal Women

Ningjian Wang, MD, PhD*; Hongfang Shao, MD*; Yi Chen, MD*; Fangzhen Xia, PhD; Chen Chi, MD; Qin Li, MD, PhD; Bing Han, MD, PhD; Yincheng Teng, MD, PhD; Yingli Lu, MD, PhD

Background—Cardiovascular disease is the leading cause of mortality in postmenopausal women. Follicle-stimulating hormone (FSH) shows negative associations with obesity and diabetes mellitus in postmenopausal women. We aimed to study the associations between FSH and 10-year risk of atherosclerotic cardiovascular disease (ASCVD) in postmenopausal women.

Methods and Results—SPECT-China (the Survey on Prevalence in East China for Metabolic Diseases and Risk Factors) is a 22-site, population-based study conducted during 2014–2015. This study included 2658 postmenopausal women. A newly developed effective tool for 10-year ASCVD risk prediction among Chinese was adopted. Regression analyses were performed to assess the relationship among FSH, 10-year ASCVD risk, and multiple cardiometabolic risk factors. With the increase in FSH quartiles, the mean 10-year ASCVD risk in postmenopausal women decreased from 4.9% to 3.3%, and most metabolic parameters were significantly ameliorated (all *P* for trend <0.05). In regression analyses, a 1-SD increment in ln-FSH was negatively associated with continuous (B −0.12, 95% confidence interval, −0.16, −0.09, *P*<0.05) and categorical (odds ratio 0.65, 95% confidence interval, 0.49, 0.85, *P*<0.05) 10-year ASCVD risk. These significant associations existed in subgroups with or without medication use, obesity, diabetes mellitus, hypertension, and dyslipidemia. Body mass index and waist circumference (both B −0.35, 95% confidence interval, −0.40, −0.30, *P*<0.05) had the largest associations of all metabolic measures, and blood pressure had the smallest association.

Conclusions—Serum FSH levels were negatively associated with 10-year ASCVD risk in postmenopausal women. Among cardiometabolic factors, obesity indices had the largest associations with FSH. These results indicated that a low FSH might be a risk factor or a biomarker for cardiovascular disease risk in postmenopausal women. **(*J Am Heart Assoc.* 2017;6:e005918. DOI: 10.1161/JAHA.117.005918.)**

Key Words: cardiovascular disease risk factors • endocrinology • follicle-stimulating hormone • menopause

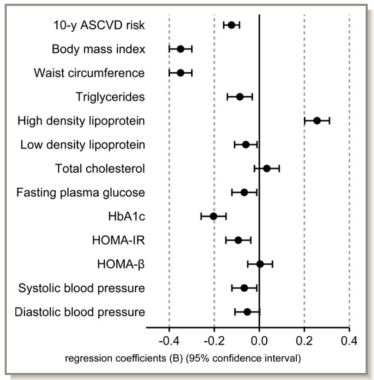

Figure 2. Associations of follicle-stimulating hormone with 10-y ASCVD risk and cardiometabolic measures in postmenopausal women. They were analyzed using linear regression models with each measure as the outcome and follicle-stimulating hormone as the explanatory variable. To facilitate comparisons across parameters, association magnitudes are reported in SD units of parameters per 1-SD increment in ln-follicle-stimulating hormone. The model controls for age, total testosterone, estradiol, luteinizing hormone, economic status, and body mass index (but not included for body mass index and waist circumference in regression model). The results are expressed as unstandardized coefficients (95% confidence interval). ASCVD indicates atherosclerotic cardiovascular disease; HbA1c, glycated hemoglobin; HOMA-IR, homeostasis model assessment index of insulin resistance.

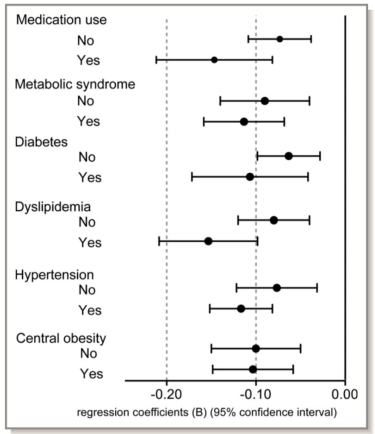

Figure 3. Subgroup analyses of associations between follicle-stimulating hormone and 10-y atherosclerotic cardiovascular disease (ASCVD) risk in postmenopausal women. Medication use included lipid-, glucose-, and blood pressure–lowering drugs and cortisone (n=552). Association magnitudes are reported in SD units of 10-y ASCVD risk per 1-SD increment in follicle-stimulating hormone. Linear regression analysis was used. The model controls for age, total testosterone, estradiol, luteinizing hormone, economic status and body mass index. The results are expressed as unstandardized coefficients (95% confidence interval).

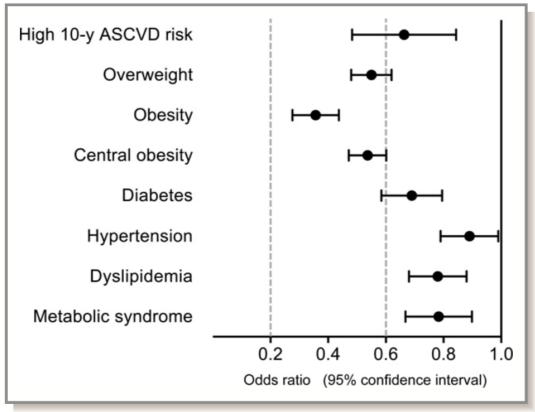

Figure 4. Associations of follicle-stimulating hormone with high 10-y ASCVD risk and metabolic diseases in postmenopausal women. They were analyzed using logistic regression models with each disease as the outcome and follicle-stimulating hormone as the explanatory variable. Adjusted ORs for each 1-SD increment of ln-follicle-stimulating hormone associated with corresponding diseases are shown. The model controls for age, total testosterone, estradiol, luteinizing hormone, economic status, and body mass index (but not included for overweight, obesity, and central obesity in regression model). The results were expressed as odds ratios (95% confidence interval). ASCVD indicates atherosclerotic cardiovascular disease; OR, odds ratio.

Table 2. Associations Between FSH Quartiles and 10-Year ASCVD Risk in Postmenopausal Women

	FSH				
	Q1	Q2	Q3	Q4	*P* for Trend
ln-(10-y ASCVD risk)	0.22 (0.15, 0.29)	0.11 (0.05, 0.17)	0.10 (0.04, 0.15)	0.00 (Ref)	<0.001
High 10-y ASCVD risk	4.22 (1.90, 9.36)	2.09 (1.00, 4.37)	2.42 (1.22, 4.80)	1.00 (Ref.)	<0.01

Data are unstandardized coefficients (95% confidence interval) for ln-(10-y ASCVD risk) and odds ratio (95% confidence interval) for high 10-y ASCVD risk. Linear and logistic regression analyses were used. The model controls for age, total testosterone, estradiol, luteinizing hormone, economic status, and body mass index. ASCVD indicates atherosclerotic cardiovascular disease; FSH, follicle-stimulating hormone.

Effetti extra-gonadici dell'FSH

MINI-REVIEW

Extragonadal Actions of FSH: A Critical Need for Novel Genetic Models

T. Rajendra Kumar[1]

Table 1. A Summary of Extragonadal Expression of FSHRs and Putative Actions of FSH

Species	Extragonadal Tissue/ Cell Tissue Type	FSH Action Noted	Reference
Mouse	Bone (osteoclasts)	Bone resorption	Sun *et al.* (9)
Human	Umbilical vein endothelial cells, placenta	Angiogenesis	
Human and mouse	Female reproductive tract	Myometrial contractility	Stilley *et al.* (10, 11)
Human	Liver (hepatocytes)	Regulation of LDLR levels	Song *et al.* (25)
Chicken	Adipose	Stimulation of lipid biosynthesis	Cui *et al.* (35)
Human and mouse	Adipose	Beiging and mitochondrial biogenesis, activation of brown adipose tissue and enhances thermogenesis	Liu *et al.* (14, 36)

Nuovi studi sono necessari per definire il ruolo in fisiologia e in patologia degli effetti extra-gonadici dell'FSH (anche considerando l'insufficienza ovarica precoce, il ruolo di inibine e activine, le differenze di genere e l'effetto della glicosilazione)