Trattamento dell'ipogonadismo con testosterone: vantaggi o svantaggi?

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Table 1 Summary of gender differences, androgen and anti-androgen treatments in cardiovascular diseases.

CVDs	Gender Difference	Androgen or anti-androgen treatments in clinical outcomes	Reference
Hypertension	Males have higher blood pressure than females	Androgen treatments increase blood pressure in male patients	27, 29, 30, 32
Stroke	Males have higher incidence in stroke than females	Gonadotropin releasing hormone agonist treatment increases stroke incidence in prostate cancer patients, but orchiectomy combined with androgen blockage and oral anti-androgen failed to show significant elevation in stroke incidence	68, 70, 71, 165, 191
Atherosclerosis	Males have thicker intima-media in early carotid atherosclerosis than females	Androgen deprivation therapy in patients with prostate cancer resulted in increased atherosclerosis	3, 79, 83, 84
Abdominal aortic aneurysm	Males have higher incidence than females	N/A	116-118
Myocardial hypertrophy	Males are at greater risk for myocardial hypertrophy than age-matched females	N/A	84, 130, 131
Myocardial infarction	Females develop more severe myocardial infarction than males	Gonadotropin releasing hormone agonist treatmen increases the risk of incident myocardial infarction and sudden cardiac death	84, 129, 161-163

N/A, data not available.

J Endocrinol 2016 Apr; 229(1); R1-R16

J Endocrinol Invest. 2015 Jan;38(1):103-12. doi: 10.1007/s40618-014-0155-9. Epub 2014 Nov 11.

Outcomes of androgen replacement therapy in adult male hypogonadism: recommendations from the Italian society of endocrinology.

Isidori AM[1], Balercia G[2], Calogero AE[3], Corona G[4], Ferlin A[5], Francavilla S[6], Santi D[7], Maggi M[8].

Cardiovascular outcomes

7.

We suggest that clinicians exercise caution in giving *T* to older men with known cardiovascular disease (CVD), due to an unclear benefit/risk ratio (2 ØØOO).

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In patients deserving treatment, we suggest offering long-acting injectable *T* esters or transdermal preparations rather than short-acting *T* esters, to minimise the risk of increased haematocrit, a potential cardiovascular risk factor (2 ØOOO).

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We suggest considering TS for middle-aged HG men with metabolic disorders without known CVD, to decrease the risk of future cardiovascular events (2 ØOOO).

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We recommend against TS to improve cardiac dysfunction in HG men (1 ØOOO).

1066 ENDOCRINE PRACTICE Vol 21 No. 9 September 2015

AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS AND AMERICAN COLLEGE OF ENDOCRINOLOGY POSITION STATEMENT ON THE ASSOCIATION OF TESTOSTERONE AND CARDIOVASCULAR RISK

Neil Goodman, MD, FACE[1]; Andre Guay, MD, FACE[2,]; Paresh Dandona, MD, PhD, FACE[3]; Sandeep Dhindsa, MD[4]; Charles Faiman, MD, MACE[5]; Glenn R. Cunningham, MD[6]; for the AACE Reproductive Endocrinology Scientific Committee*

CONCLUSION

Testosterone therapy can provide significant benefits for hypogonadal men. As recently concluded in an extensive review of literature, there is no compelling evidence that testosterone therapy increases cardiovascular risk (37). Indeed, the FDA concluded that the "signal of cardiovascular risk is weak." We agree with their recommendation that large-scale prospective, randomized controlled trials on testosterone therapy, focusing on cardiovascular benefits and risks, are clearly needed. The Institute of Medicine also recommended that studies be done to determine if TRT is efficacious and safe in older men. The National Institute of Aging is funding a relatively large trial to address this issue, and results should be available later in 2015. While safety issues are being addressed, the study is not powered to determine if TRT will increase the risk of prostate cancer or cardiovascular events. If the ongoing studies determine that there is a benefit in treating symptomatic older men, a much larger trial will need to be funded and conducted to assess potential risk. In the interim, clinical decisions on TRT, based on appropriate clinical and laboratory assessment, will need to be individualized and discussed with each and every patient. It needs to be emphasized that low testosterone is often a marker for chronic disease, and the underlying cardiovascular disease risk factors should be addressed. In patients with vascular disease and minor symptoms of hypogonadism, a more cautious approach towards testosterone therapy is prudent. Physicians should have a detailed discussion with such patients about the above-mentioned reports before embarking on testosterone replacement.

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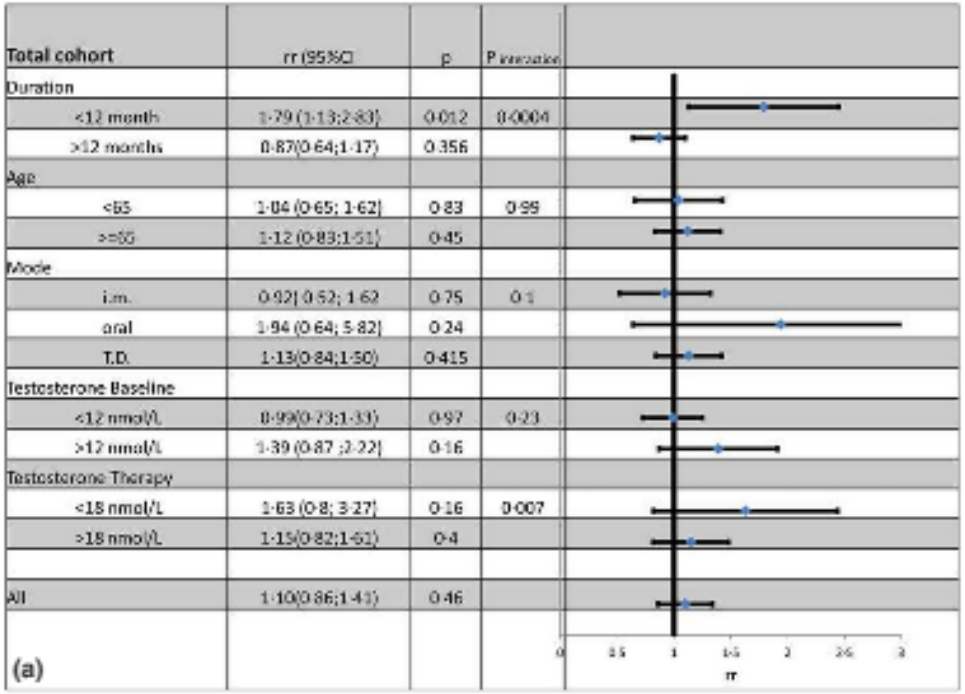
ORIGINAL ARTICLE

Testosterone therapy, association with age, initiation and mode of therapy with cardiovascular events: a systematic review

Stewart G. Albert* and John E. Morley*†

*Department of Internal Medicine, Division of Endocrinology, and †Department of Internal Medicine, Division of Geriatrics, Saint Louis University School of Medicine, St. Louis, MO, USA



Total cohort	rr (95%CI	p	P interaction
Duration			
<12 month	1·79 (1·13;2·83)	0·012	0·0004
>12 months	0·87(0·64;1·17)	0·356	
Age			
<65	1·04 (0·65; 1·62)	0·83	0·99
>=65	1·12 (0·83;1·51)	0·45	
Mode			
i.m.	0·92(0·52; 1·62	0·75	0·1
oral	1·94 (0·64; 5·82)	0·24	
T.D.	1·13(0·84;1·50)	0·415	
Testosterone Baseline			
<12 nmol/L	0·99(0·73;1·33)	0·97	0·23
>12 nmol/L	1·39 (0·87 ;2·22)	0·16	
Testosterone Therapy			
<18 nmol/L	1·63 (0·8; 3·27)	0·16	0·007
>18 nmol/L	1·15(0·82;1·61)	0·4	
All	1·10(0·86;1·41)	0·46	

(a)

Summary

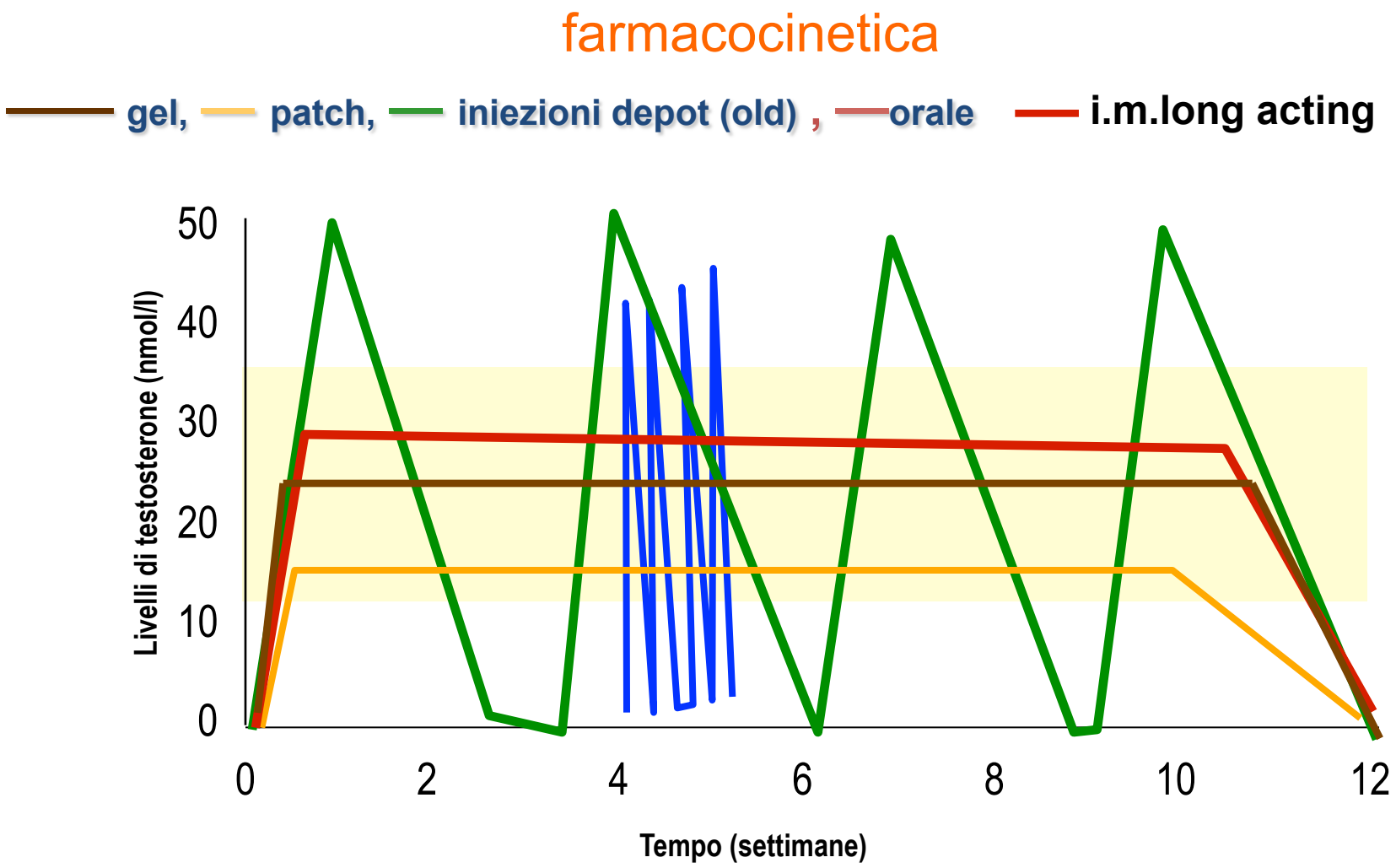
Background Although male hypogonadism is associated with increased cardiovascular events (CVE), recent concerns are that testosterone supplementation may increase CVE. The purpose was to determine associations with age, initiation or mode of therapy to explain these discrepancies.

Data synthesis Meta-analyses were supplemented through Scopus and PubMed with search terms 'testosterone', 'random' and 'trial'. CVE, defined before data extraction, were death, myocardial infarction, acute coronary syndrome, percutaneous coronary intervention, coronary bypass, syncope, arrhythmia, hospital admission for congestive heart failure or cerebrovascular event.

Results There were 45 trials with 5328 subjects evaluated, with a mean age of 63·3 (SD ±7·9) years, followed for mean study duration of 10·6 (± 8·6) months. Overall, testosterone supplementation was not associated with increased CVE risk ratio (rr = 1·10 (95% CI 0·86; 1·41, $P = 0·45$)). However, there was an increase event rate during the first 12 months (rr = 1·79 (1·13;2·83, $P = 0·012$)), predominantly in those ≥65 years, (rr = 2·90 (1·35;6·21, $P = 0·006$)). Within studies with lipid data, CVE were associated with fall in HDL, $P = 0·002$. Intramuscular testosterone appeared neutral for CVE (rr = 0·96 (0·462;1·98, $P = 0·91$)) compared with oral testosterone (rr = 2·28 (95% CI 2·28;8·59, $P = 0·22$)) and transdermal testosterone (rr = 2·80 (1·38;5·68, $P = 0·004$)). Intramuscular testosterone had the least effect of lowering HDL and non-HDL cholesterol (both $P < 0·001$).

Conclusions Testosterone supplementation may be associated with increased CVE in those ≥65 years especially during the first year. Biological actions may differ depending upon mode of testosterone administration with intramuscular testosterone having less cardiovascular risk.

Differenti formulazioni



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World J Mens Health 2015 December 33(3): 130-142
http://dx.doi.org/10.5534/wjmh.2015.33.3.130

Review Article

Testosterone Replacement Therapy and Cardiovascular Risk: A Review

Giovanni Corona G[1], Giulia Rastrelli[2], Elisa Maseroli[2], Alessandra Sforza[1], Mario Maggi[2]

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Recent reports in the scientific and lay press have suggested that testosterone (T) replacement therapy (TRT) is likely to increase cardiovascular (CV) risk. In a final report released in 2015, the Food and Drug Administration (FDA) cautioned that prescribing T products is approved only for men who have low T levels due to primary or secondary hypogonadism resulting from problems within the testis, pituitary, or hypothalamus (e.g., genetic problems or damage from surgery, chemotherapy, or infection). In this report, the FDA emphasized that the benefits and safety of T medications have not been established for the treatment of low T levels due to aging, even if a man's symptoms seem to be related to low T. In this paper, we reviewed the available evidence on the association between TRT and CV risk. In particular, data from randomized controlled studies and information derived from observational and pharmacoepidemiological investigations were scrutinized. The data meta-analyzed here do not support any causal role between TRT and adverse CV events. This is especially true when hypogonadism is properly diagnosed and replacement therapy is correctly performed. Elevated hematocrit represents the most common adverse event related to TRT. Hence, it is important to monitor hematocrit at regular intervals in T-treated subjects in order to avoid potentially serious adverse events.

Key Words: Hematocrit; Mortality; Myocardial infarction; Testosterone

J Endocrinol Invest. 2015 Jan;38(1):103-12. doi: 10.1007/s40618-014-0155-9. Epub 2014 Nov 11.

Outcomes of androgen replacement therapy in adult male hypogonadism: recommendations from the Italian society of endocrinology.

Isidori AM[1], Balercia G[2], Calogero AE[3], Corona G[4], Ferlin A[5], Francavilla S[6], Santi D[7], Maggi M[8].

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We suggest that clinicians exercise caution in giving *T* to older men with known cardiovascular disease (CVD), due to an unclear benefit/risk ratio (2 ØØOO).

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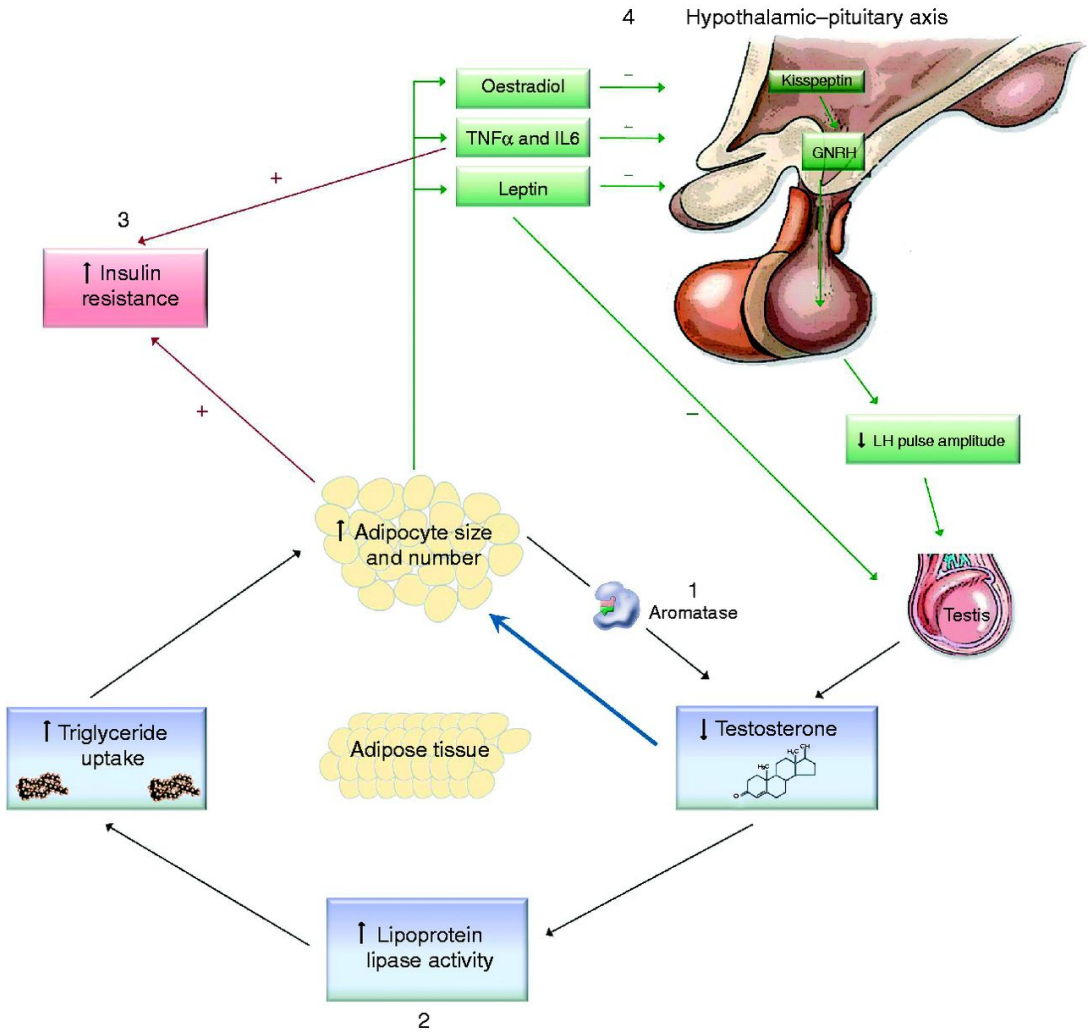

IPOGONADISMO

I livelli di androgeni diminuiscono con l'avanzare dell'età

Primario

Secondario

Da resistenza periferica

LOH

Late onset hypogonadism (LOH) is an endocrine condition characterized by a progressive reduction in serum concentrations of androgens in middle-aged men **[1]**.

The frequency of this condition, as recently reported by the study European Male Aging Study (EMAS) is 2.1% **[2]**.

Though applying only biochemical criteria, the prevalence of LOH has been reported to be up to 15% in the general population **[3]**.

REFERENCES

[1] Lunenfeld B, Mskhalaya G, Zitzmann M, Arver S, Kalinchenko S, Tishova Y, Morgentaler A. Recommendations on the diagnosis, treatment and monitoring of hypogonadism in men. Aging Male. 2015;18:5-15.

[2] Tajar A, Huhtaniemi IT, O'Neill TW, Finn JD, Pye SR, Lee DM, Bartfai G, Boonen S, Casanueva FF, Forti G, Giwercman A, Han TS, Kula K, Labrie F, Lean ME, Pendleton N, Punab M, Vanderschueren D, Wu FC; EMAS Group. Characteristics of androgen deficiency in late-onset hypogonadism: results from the European Male Aging Study (EMAS). J Clin Endocrinol Metab. 2012;97:1508-16.

[3] Buvat J, Maggi M, Guay A, Torres LO. Testosterone deficiency in men: systematic review and standard operating procedures for diagnosis and treatment. J Sex Med 2013;10:245-84.

The pathogenic mechanisms responsible for LOH can be distinguished in a central (altered hypothalamic or pituitary function) and in a peripheral form (impaired testicular function), the two mechanisms can coexist in the same patient **[4]**.

The sexual dysfunction (in particular the erectile dysfunction) represent the main symptom of LOH, with a prognostic significance.

LOH is associated with an increased cardiovascular and metabolic risk **[5]** and an increased risk of osteoporosis and depression **[6]**.

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[5] La Vignera S, Condorelli R, Vicari E, D'Agata R, Calogero A. Original immunophenotype of blood endothelial progenitor cells and microparticles in patients with isolated arterial erectile dysfunction and late onset hypogonadism: effects of androgen replacement therapy. Aging Male. 2011;14:183-9.

[6] Almehmadi Y1, Yassin DJ, Yassin AA. Erectile dysfunction is a prognostic indicator of comorbidities in men with late onset hypogonadism. Aging Male. 2015 Jun 1:1-9. [Epub ahead of print].

Age trends in the level of serum testosterone and other hormones in middle-aged men: longitudinal results from the Massachusetts male aging study

Feldman HA, Longcope C, Derby CA, Johannes CB, Araujo AB, Coviello AD, Bremner WJ, McKinlay JB

Prospective, **population**-based study (1,709 Caucasian men)

7-10 years of follow-up in 1,156 subjects

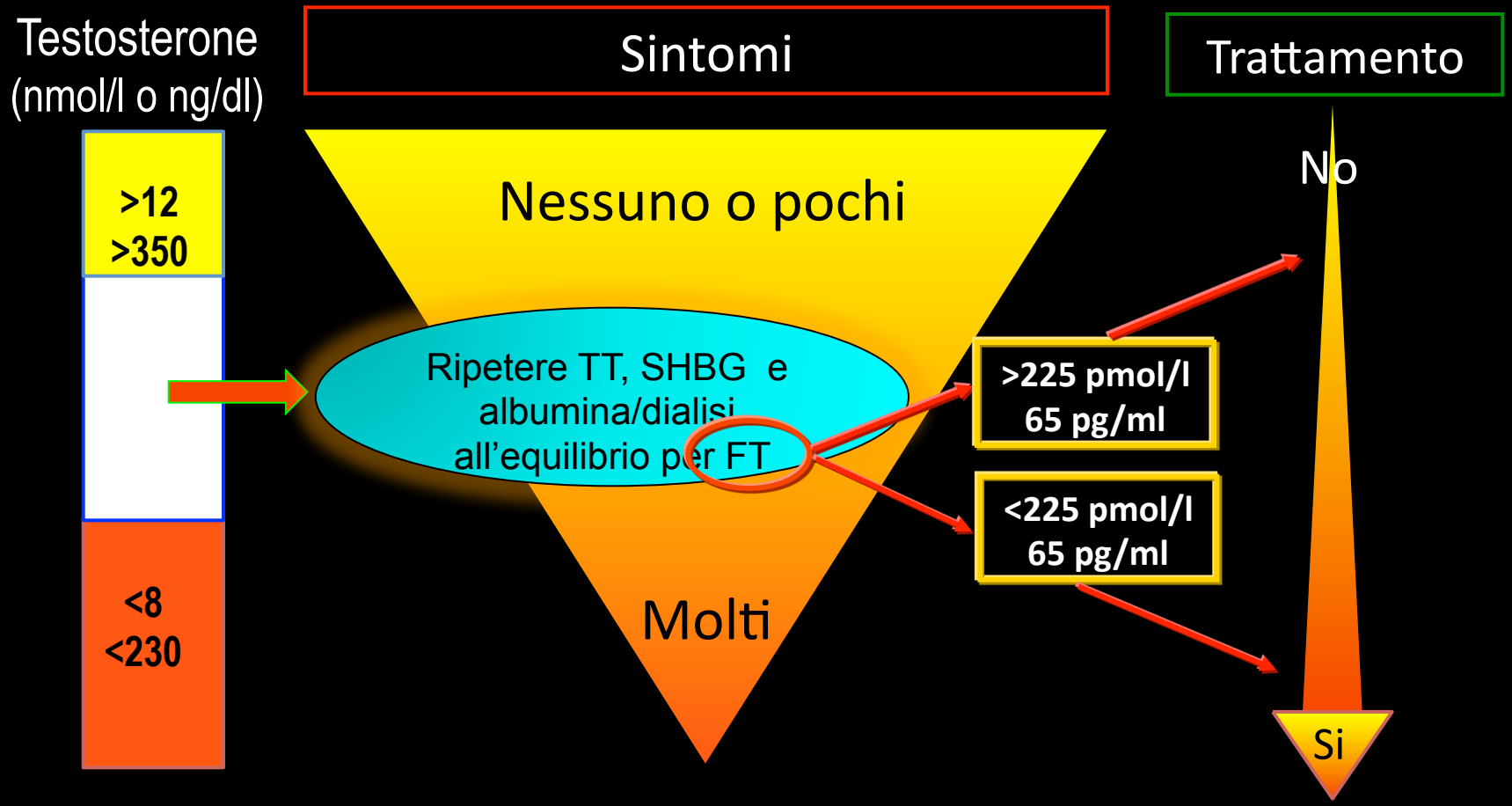
Aged 40–70 years at study entry

Hormone	Estimated annual variation
Total testosterone	-1.6%
SHBG	+1.3%
Free testosterone	-2.8%
Albumin-bound testosterone	-2.5%
DHT	+3.5%
DHEA	-1.4%
DHEAS	-2.2%
E1	-3.6%
Androstendiol	-0.4%

JCEM 86:589-598, 2002

Diagnosi di LOH

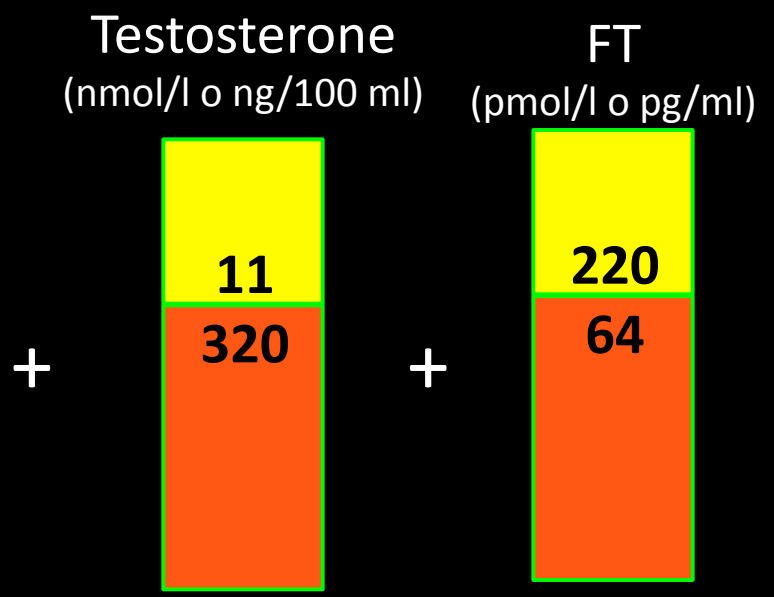
ISA, ISSAM, EAU e ASA linee guida (Wang et al., 2009)



Diagnosi di LOH

European Male Aging study

Sintomi	Segni
Riduzione della massa e della forza muscolare	Riduzione della densità minerale ossea/ osteoporosi
Riduzione delle erezioni mattutine (T<11 nmol/l)	Aumento dell'obesità
Disfunzione erettile di vario grado (T<8,5 nmol/l)	Aumento della circonferenza vita
Riduzione della frequenza di pensieri sessuali (T<8 nmol/l)	Regressione dei caratteri sessuali secondari
Riduzione della libido	Riduzione dell'emopoiesi
Depressione/decadi-mento cognitivo	
Riduzione della qualità di vita	



Nessun sintomo è specifico

Wu et al., NEJM 363:123-135, 2010

Testosterone: a vascular hormone in health and disease

Journal of Endocrinology
(2013) **217**, R47–R71

Figure 3

Potential mechanisms by which testosterone influences vascular reactivity. Endothelium-independent mechanisms of testosterone are considered to occur primarily via the inhibition of voltage-operated Ca^{2+} channels (VOCCs) and/or activation of K^+ channels (KCs) on smooth muscle cells (SMCs). Testosterone shares the same molecular binding site as nifedipine on the α1-C subunit of L-type Ca^{2+} channels to cause channel blockade at physiological concentrations, thus restricting Ca^{2+} influx and inducing vasodilation (1). Some reports suggest that pharmacological concentrations of testosterone can activate Ca^{2+} channel opening and induce vasoconstriction through enhanced Ca^{2+} influx. Alternatively, testosterone activates voltage-operated K^+ channels and/or large-conductance, Ca^{2+}-activated K^+ channels, increasing intracellular K^+ efflux to induce hyperpolarisation and subsequent vasorelaxation (2). Testosterone may also inhibit intracellular Ca^{2+} influx via store-operated Ca^{2+} channels (SOCCs) by blocking response to prostaglandin F2α (PGF2α) (3). Endothelium-dependent actions of testosterone may be long-term genomic and non-genomic effects. Testosterone increases the expression of endothelial nitric oxide synthase (eNOS) and enhances nitric oxide (NO) production (4). Whether these actions are via direct androgen receptor binding, aromatisation to oestradiol and oestrogen receptor activation, or interaction with alternative intracellular signalling pathways remains unknown. Additionally, testosterone treatment has been shown to increase eNOS activity by enhancing phosphorylation potentially via the non-genomic activation of intracellular signalling pathways and Ca^{2+} influx (5). Increased NO acts on SMCs to induce vasorelaxation by activating cGMP, which in turn activates cGMP-dependent protein kinases (PKG) (6). PKG phosphorylates and activates sarcoplasmic reticulum Ca^{2+}-ATPase (SERCA), which increases the uptake of Ca^{2+} into the superficial sarcoplasmic reticulum (SR) and therefore decreases global cell Ca^{2+}. PKG also increases Ca^{2+} release into the submembrane space where the activation of K^+ channels ensues and PKG may additionally inhibit Ca^{2+} channel activity directly to cause vasorelaxation. T, testosterone.

Journal of Endocrinology (2013) **217**, R47–R71

J Sex Med. 2010 Apr;7(4 Pt 1):1557-64. doi: 10.1111/j.1743-6109.2009.01690.x. Epub 2010 Jan 25.

Low testosterone is associated with an increased risk of MACE lethality in subjects with erectile dysfunction.

Corona G[1], Monami M, Boddi V, Cameron-Smith M, Fisher AD, de Vita G, Melani C, Balzi D, Sforza A, Forti G, Mannucci E, Maggi M.

Author information

Abstract

INTRODUCTION: Although testosterone (T) has been suggested to play a protective role against the development of atherosclerosis, studies demonstrating an association between low T and incident major adverse cardiovascular events (MACE) are scanty in the general population and absent in subjects with erectile dysfunction (ED).

AIM: To investigate whether low T in subjects with ED predict incident fatal or nonfatal MACE.

METHODS: This is an observational prospective cohort study evaluating a consecutive series of 1687 patients attending our andrological unit for ED. Patients were interviewed using the structured interview on erectile dysfunction (SIEDY) and ANDROTEST structured interviews measuring components relative to ED and hypogonadal-related symptoms, respectively.

MAIN OUTCOME MEASURES: Total T was evaluated at baseline. Information on MACE was obtained through the City of Florence Registry Office.

RESULTS: Among the patients studied, 5.2, 13.8, and 22.4% were hypogonadal according to different thresholds (T < 8, 10.4 and 12 nmol/L or 230, 300 and 350 ng/dL, respectively). During a mean follow-up of 4.3 + or - 2.6 years, 139 MACE, 15 of which were fatal, were observed. Unadjusted incidence of MACE was not associated with T levels. Conversely, the proportion of lethal events among MACE was significantly higher in hypogonadal patients, using either 10.4 nmol/L (300 ng/dL) or 8 nmol/L (230 ng/dL) thresholds. However, after adjustment for age and Chronic Diseases Score in a Cox regression model, only the association between incident fatal MACE and T < 8 nmol/L (230 ng/dL) was confirmed (HR = 7.1 [1.8-28.6]; P < 0.001). Interestingly, measuring hypogonadal-related symptoms and signs through ANDROTEST, only fatal MACE were also associated with a higher score (HR = 1.2 [1.0-1.5] for each ANDROTEST score increment; P = 0.05 after adjustment for age and Chronic Diseases Score).

CONCLUSIONS: T levels are associated with a higher mortality of MACE. The identification of low T levels should alert the clinician thus identifying subjects with an increased cardiovascular risk.

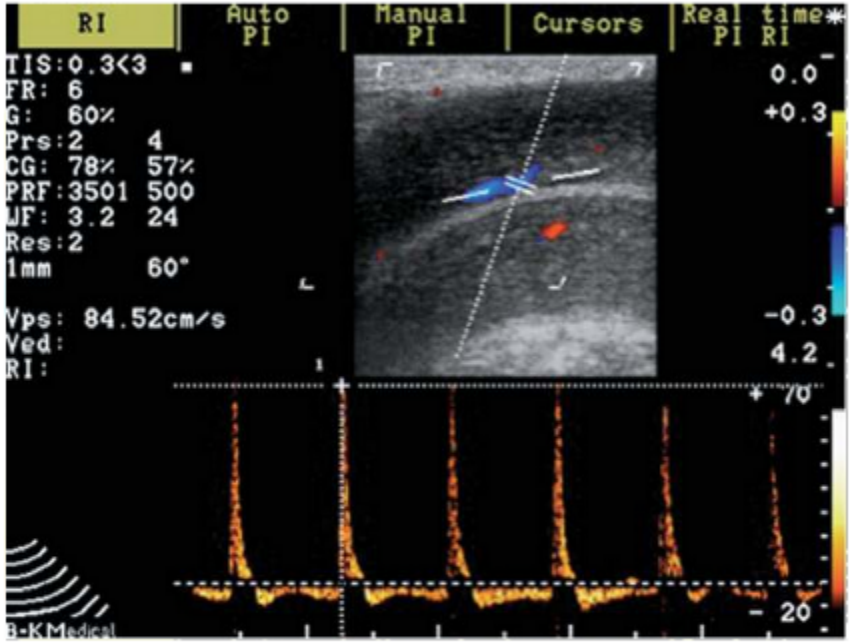


Figure 1 Real-time Doppler ultrasound scan with B-mode image of right cavernosal artery showing normal peak systolic velocity of 84.5 cm/second at peak erection response, suggesting a nonvascular etiology

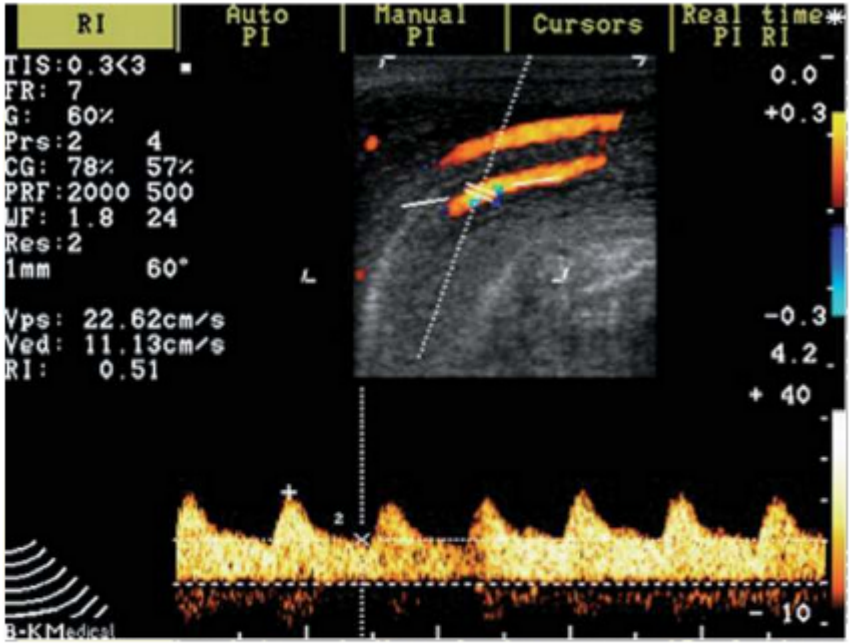
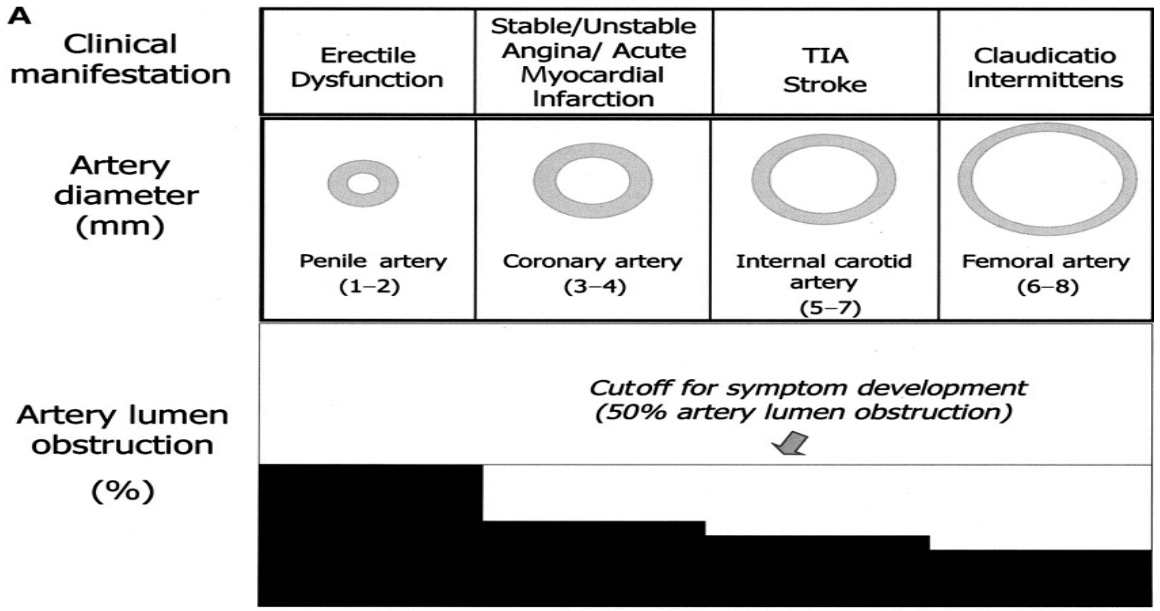


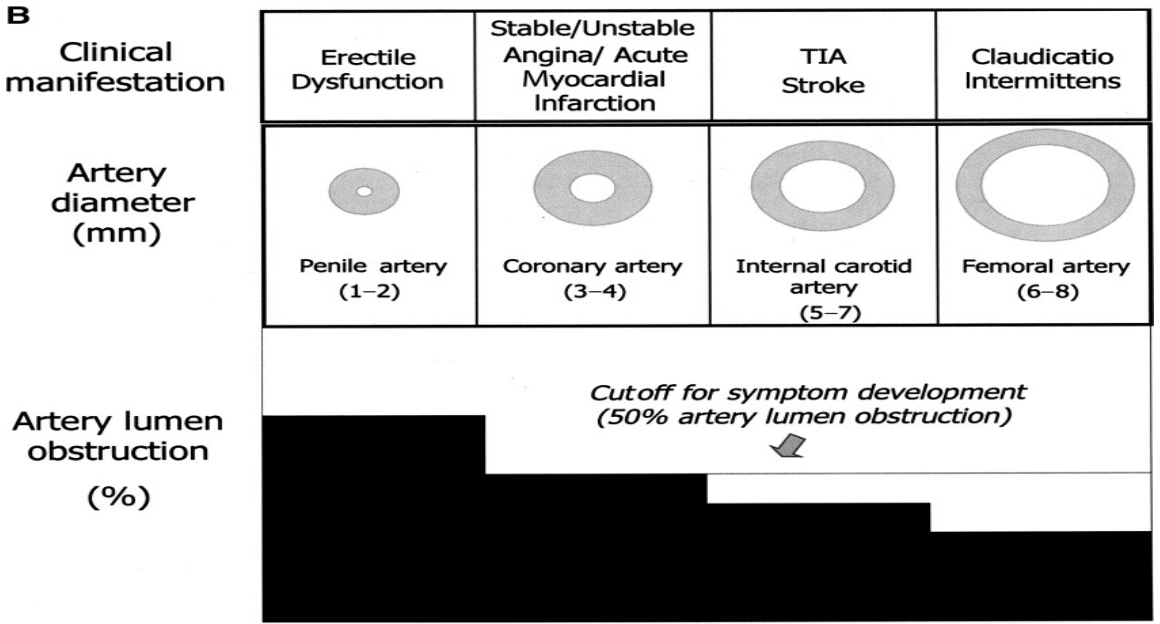
Figure 2 Real-time Doppler ultrasound scan with left cavernosal arterial blood flow with <25 cm/second Vps, end-diastolic velocity (Ved) of >11 cm/second, and resistive index of 0.51, suggesting a mixed vascular etiology

Am J Cardiol. 2005 Dec 26;96(12B):19M-23M. Epub 2005 Nov 4.

The artery size hypothesis: a macrovascular link between erectile dysfunction and coronary artery disease.

Montorsi P[1], Ravagnani PM, Galli S, Rotatori F, Briganti A, Salonia A, Rigatti P, Montorsi F.





A Systematic Review of the Association Between Erectile Dysfunction and Cardiovascular Disease

[13] Montorsi F, Briganti A, Salonia A, et al. Erectile dysfunction prevalence, time of onset and association with risk factors in 300 consecutive patients with acute chest pain and angiographically documented coronary artery disease. Eur Urol 2003;44:360–5, discussion 364–5.

DATI CROSS SECTIONAL RETROSPETTICI

3.2. *Erectile dysfunction as a predictor of cardiovascular disease*

3.2.1. *Cross-sectional and retrospective studies*

Based on experimental data and a common pathophysiologic background, several researchers tried to prove causality between ED and CVD. Early retrospective studies investigated the prevalence of ED in CVD patients and showed an increased risk of ED in patients with CVD [10–12]. The first compelling evidence of an association between ED and coronary artery disease (CAD) came from the pioneering study by Montorsi et al. [13]. The authors reported that roughly 50% of patients with acute chest pain and angiographically documented CAD experienced ED. Sexual dysfunction preceded CAD in almost 70% of cases, becoming clinically evident >3 yr before coronary symptoms and thus implying a temporal association between ED and CAD. These data highlighted the possible common pathologic link between these two conditions, proposing ED as a biomarker for subsequent symptomatic CAD [13]. The bidirectional association between ED and CAD was supported by another angiographic study by Vlachopoulos et al., in which almost 20% of ED patients were diagnosed with asymptomatic CAD [14].

Eur Urol. 2005 Mar;47(3):409-16; discussion 416. Epub 2004 Dec 18.

Testosterone regulates PDE5 expression and in vivo responsiveness to tadalafil in rat corpus cavernosum.

Zhang XH[1], Morelli A, Luconi M, Vignozzi L, Filippi S, Marini M, Vannelli GB, Mancina R, Forti G, Maggi M.

Author information

Abstract

OBJECTIVES: To investigate the effect of testosterone on PDE5 expression and PDE5 inhibitor tadalafil in vivo responsiveness in a rat model.

METHODS: PDE5 expression was localized by immunohistochemistry in the rat corpus cavernosum (CC) and quantified by both real-time RT-PCR and Western blot analysis in several tissues. In the in vivo study, control, castrated and testosterone (T) supplemented castrated rats were treated with acute or chronic oral tadalafil. Erectile function was evaluated by monitoring intracavernous pressure (ICP) following electro-stimulation (ES) of the cavernous nerve and intracavernous injection of NO donor, sodium nitroprusside (SNP).

RESULTS: Rat CC expressed the highest PDE5 mRNA level. PDE5 was specifically immunolocalized in endothelial and smooth muscle cells. Surgical castration induced a significant reduction of PDE5 gene and protein expression ($p<0.05$), and ES response at all stimulation frequencies ($p<0.001$). T supplementation completely restored PDE5 expression, erectile response to ES and responsiveness to PDE5 inhibitor. Both acute and chronic tadalafil treatment were ineffective in ameliorating the ES response in castrated rats. Injection of increasing concentrations of SNP in castrated rats resulted in a statistically significant increase in ICP/MAP ratio as that observed in intact rats. In addition, tadalafil did not amplify the SNP effect in castrated rats at all the doses tested (0.06-6 nmoles).

CONCLUSIONS: Our findings demonstrate that testosterone positively regulates PDE5 expression and in vivo responsiveness to PDE5 inhibitor, tadalafil, in the rat CC.

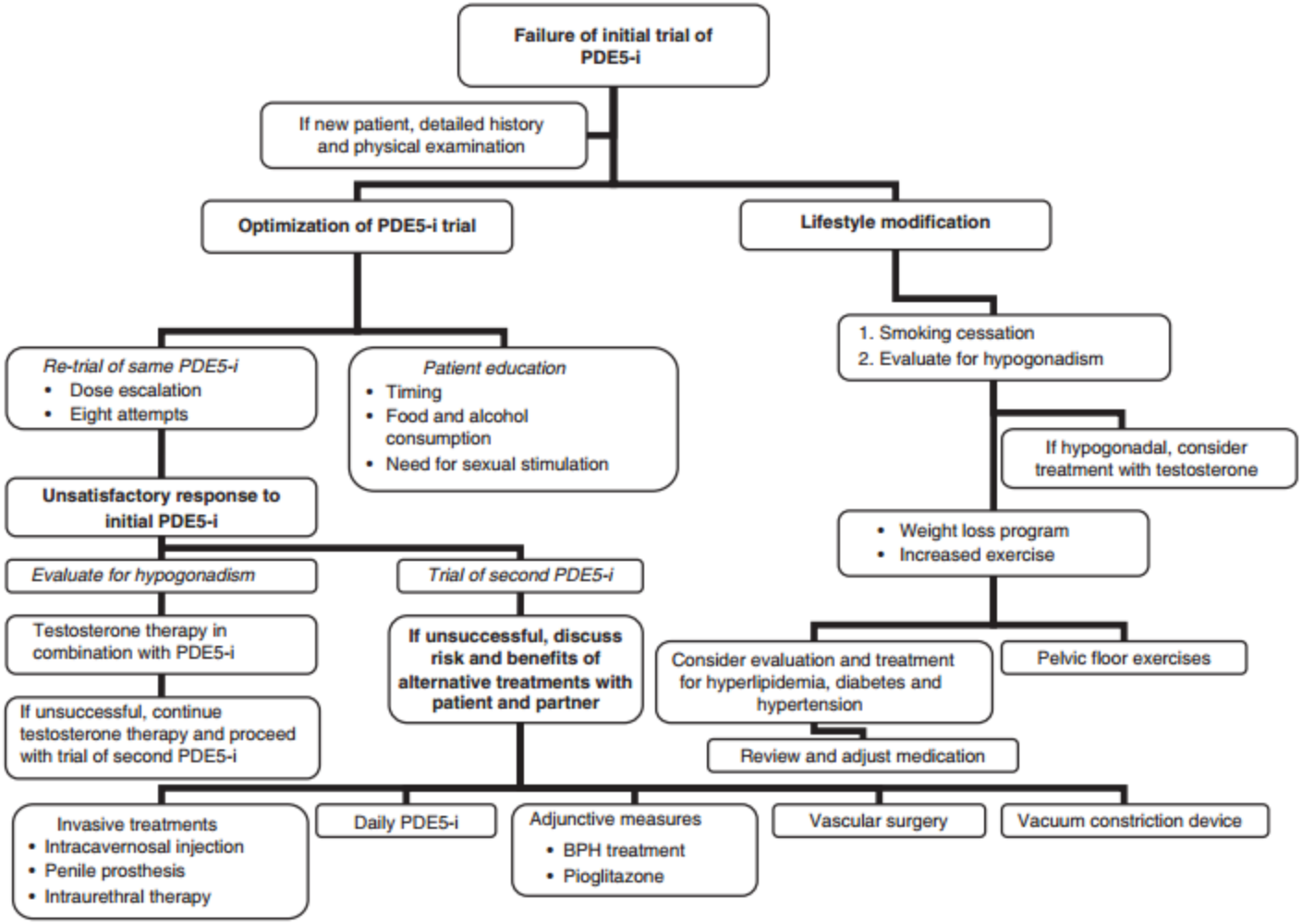


Figure 1. Proposed noninvasive treatment strategy.

Endothelial Antioxidant Administration Ameliorates the Erectile Response to PDE5 Regardless of the Extension of the Atherosclerotic Process

Enzo Vicari, MD, Sandro La Vignera, MD, Rosita Condorelli, MD, and Aldo Eugenio Calogero, MD

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DOI: 10.1111/j.1743-6109.2009.01420.x

ABSTRACT

Introduction. The lack of phosphodiesterase type 5 inhibitor effects in patients with erectile dysfunction (ED) of arterial origin may be caused by an endothelial dysfunction that causes a series of biochemical alterations leading to a reduced nitric oxide (NO) bioavailability and increased oxidative stress.

Aim. The aim of this study was to evaluate the effects of the treatment with endothelial antioxidant compounds (EAC) on the erectile response to sildenafil in patients with arterial ED already treated with sildenafil (100 mg twice a week for 8 weeks).

Mean Outcome Measures. A patient was considered responsive when the 5-item International Index of Erectile Function questionnaire score increased by >5 points.

Methods. Fifty-three patients with arterial ED, hypertension, and diabetes mellitus were randomly given, for 8 weeks, EAC (1 dose/day) and, after a wash out of 8 weeks, sildenafil (100 mg) plus EAC. The patients were divided into the following four groups: A (N = 12): patients with ED alone; B (N = 14): patients with ED plus atheromasic plaques and/or increased intima-media thickness of common carotid arteries; C (N = 14): patients with ED plus lower limb artery abnormalities; and D (N = 13): patients with ED plus carotid and lower limb artery abnormalities.

Results. The administration of EAC plus sildenafil resulted in a significantly higher number of responsive patients (N = 36, 68%) compared with sildenafil alone (N = 24, 45%) or EAC alone (N = 17, 32%). The percentage of patients who successfully responded to the combined treatment increased in the various groups. It was 83%, 64%, 71%, and 54%, respectively, for groups A, B, C, and D. Furthermore, patients treated with EAC and sildenafil reached a successful response in a shorter length of time (3 weeks) compared with patients responsive to sildenafil (5.2 weeks) or EAC (5.7 weeks) alone.

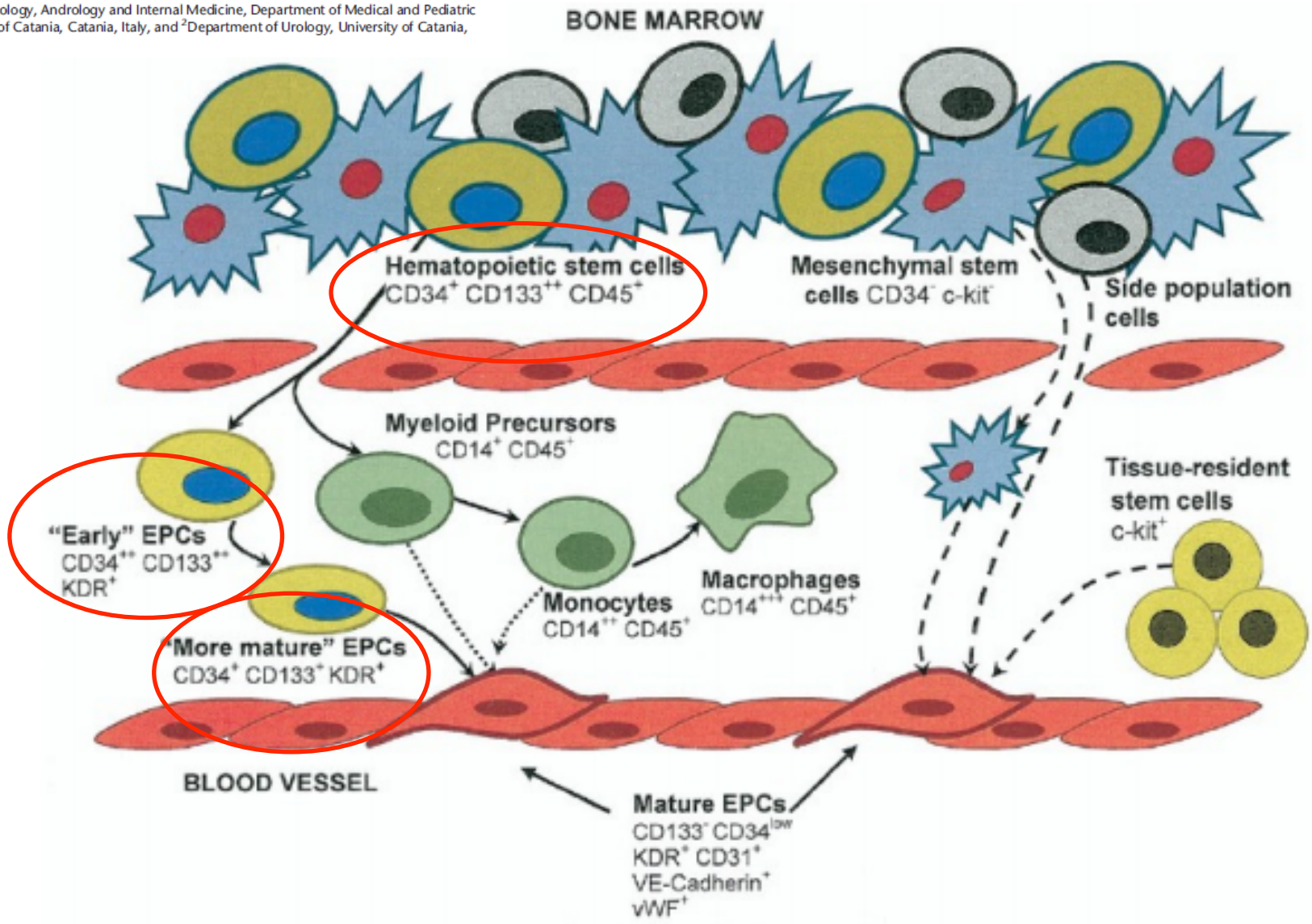
Conclusion. EAC administration to patients with arterial ED improved the success rate to sildenafil. These data suggest that, in such patients, a combined treatment may be considered to increase bioavailable NO and to neutralize radical oxygen species, which in turn inactive NO. **Vicari E, La Vignera S, Condorelli R, and Calogero AE. Endothelial antioxidant administration ameliorates the erectile response to PDE5 regardless of the extension of the atherosclerotic process. J Sex Med 2010;7:1247–1253.**

Key Words. Erectile Dysfunction; Sildenafil; Antioxidant; IIEF; Endothelium

Vascular regenerative therapies for the treatment of erectile dysfunction: current approaches

[1]R. A. Condorelli, [1]A. E. Calogero, [1]E. Vicari, [2]V. Favilla, [2]G. Morgia, [2]S. Cimino and [1]S. La Vignera

[1]Section of Endocrinology, Andrology and Internal Medicine, Department of Medical and Pediatric Sciences, University of Catania, Catania, Italy, and [2]Department of Urology, University of Catania, Catania, Italy



DE E IPOGONADISMO

LA PEGGIORE

ASSOCIAZIONE

POSSIBILE

1066 ENDOCRINE PRACTICE Vol 21 No. 9 September 2015

AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS AND AMERICAN COLLEGE OF ENDOCRINOLOGY POSITION STATEMENT ON THE ASSOCIATION OF TESTOSTERONE AND CARDIOVASCULAR RISK

Neil Goodman, MD, FACE[1]; Andre Guay, MD, FACE[2,]; Paresh Dandona, MD, PhD, FACE[3]; Sandeep Dhindsa, MD[4]; Charles Faiman, MD, MACE[5]; Glenn R. Cunningham, MD[6]; for the AACE Reproductive Endocrinology Scientific Committee*

CONCLUSION

Testosterone therapy can provide significant benefits for hypogonadal men. As recently concluded in an extensive review of literature, there is no compelling evidence that testosterone therapy increases cardiovascular risk (37). Indeed, the FDA concluded that the "signal of cardiovascular risk is weak." We agree with their recommendation that large-scale prospective, randomized controlled trials on testosterone therapy, focusing on cardiovascular benefits and risks, are clearly needed. The Institute of Medicine also recommended that studies be done to determine if TRT is efficacious and safe in older men. The National Institute of Aging is funding a relatively large trial to address this issue, and results should be available later in 2015. While safety issues are being addressed, the study is not powered to determine if TRT will increase the risk of prostate cancer or cardiovascular events. If the ongoing studies determine that there is a benefit in treating symptomatic older men, a much larger trial will need to be funded and conducted to assess potential risk. In the interim, clinical decisions on TRT, based on appropriate clinical and laboratory assessment, will need to be individualized and discussed with each and every patient. It needs to be emphasized that low testosterone is often a marker for chronic disease, and the underlying cardiovascular disease risk factors should be addressed. In patients with vascular disease and minor symptoms of hypogonadism, a more cautious approach towards testosterone therapy is prudent. Physicians should have a detailed discussion with such patients about the above-mentioned reports before embarking on testosterone replacement.

J Clin Endocrinol Metab. 2007 Feb;92(2):405-13. Epub 2006 Nov 7.

Position statement: Utility, limitations, and pitfalls in measuring testosterone: an Endocrine Society position statement.

Rosner W[1], Auchus RJ, Azziz R, Sluss PM, Raff H.

Author information

Abstract

OBJECTIVE: The objective of the study was to evaluate the current state of clinical assays for total and free testosterone.

PARTICIPANTS: The five participants were appointed by the Council of The Endocrine Society and charged with attaining the objective using published data and expert opinion.

EVIDENCE: Data were gleaned from published sources via online databases (principally PubMed, Ovid MEDLINE, Google Scholar), the College of American Pathologists, and the clinical and laboratory experiences of the participants.

CONSENSUS PROCESS: The statement was an effort of the committee and was reviewed in detail by each member. The Council of The Endocrine Society reviewed a late draft and made specific recommendations.

CONCLUSIONS: Laboratory proficiency testing should be based on the ability to measure accurately and precisely samples containing known concentrations of testosterone, not only on agreement with others using the same method. When such standardization is in place, normative values for total and free testosterone should be established for both genders and children, taking into account the many variables that influence serum testosterone concentration.

Eur J Endocrinol. 2012 Jun;166(6):983-91. doi: 10.1530/EJE-11-1051. Epub 2012 Mar 15.

Comparison of serum testosterone and estradiol measurements in 3174 European men using platform immunoassay and mass spectrometry; relevance for the diagnostics in aging men.

Huhtaniemi IT[1], Tajar A, Lee DM, O'Neill TW, Finn JD, Bartfai G, Boonen S, Casanueva FF, Giwercman A, Han TS, Kula K, Labrie F, Lean ME, Pendleton N, Punab M, Silman AJ, Vanderschueren D, Forti G, Wu FC; EMAS Group.

⊕ Collaborators (28)

⊕ Author information

Abstract

BACKGROUND: The limitations of serum testosterone and estradiol (E(2)) measurements using non-extraction platform immunoassays (IAs) are widely recognized. Switching to more specific mass spectrometry (MS)-based methods has been advocated, but directly comparative data on the two methods are scarce.

METHODS: We compared serum testosterone and E(2) measurements in a large sample of middle-aged/elderly men using a common platform IA and a gas chromatography (GC)-MS method, in order to assess their limitations and advantages, and to diagnose male hypogonadism. Of subjects from the European Male Aging Study (n=3174; age 40-79 years), peripheral serum testosterone and E(2) were analyzed using established commercial platform IAs (Roche Diagnostics E170) and in-house GC-MS methods.

RESULTS: Over a broad concentration range, serum testosterone concentration measured by IA and MS showed high correlation (R=0.93, P<0.001), which was less robust in the hypogonadal range (<11 nmol/l; R=0.72, P<0.001). The IA/MS correlation was weaker in E(2) measurements (R=0.32, P<0.001, at E(2) <40.8 pmol/l, and R=0.74, P<0.001, at E(2) >40.8 pmol/l). Using MS as the comparator method, IA ascertained low testosterone compatible with hypogonadism (<11 nmol/l), with 75% sensitivity and 96.3% specificity. The same parameters with IA for the detection of low E(2) (<40.7 pmol/l) were 13.3 and 99.3%, and for high E(2) (>120 pmol/l) 88.4 and 88.6%.

CONCLUSION: A validated platform IA is sufficient to detect subnormal testosterone concentrations in the diagnosis of male hypogonadism. The IA used for E(2) measurements showed poor correlation with MS and may only be suitable for the detection of high E(2) in men.

Riconoscere i pazienti con

ipogonadismo

a prescindere dalle apparenti normali

concentrazioni di testosterone totale

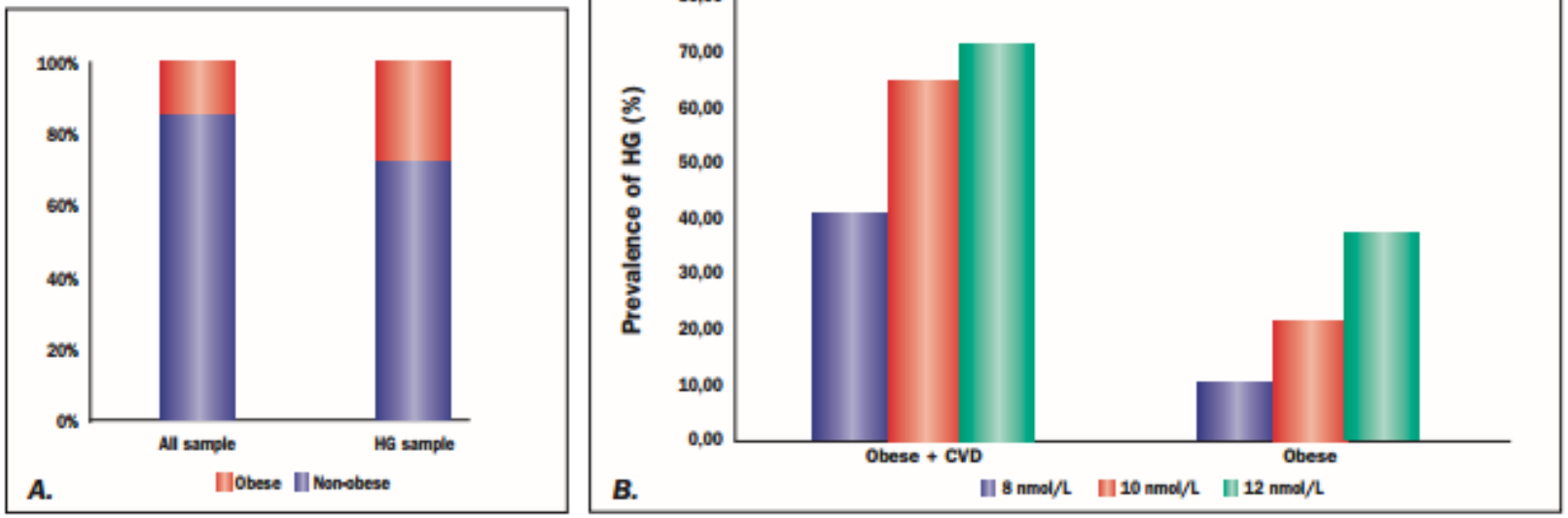
Maschere dell'ipogonadismo

Ipogonadismo maschile e obesità

Figure 5.

Panel A. *Percentage of obese and non-obese Italian men in hypogonadal sample (HG sample) and general population.*

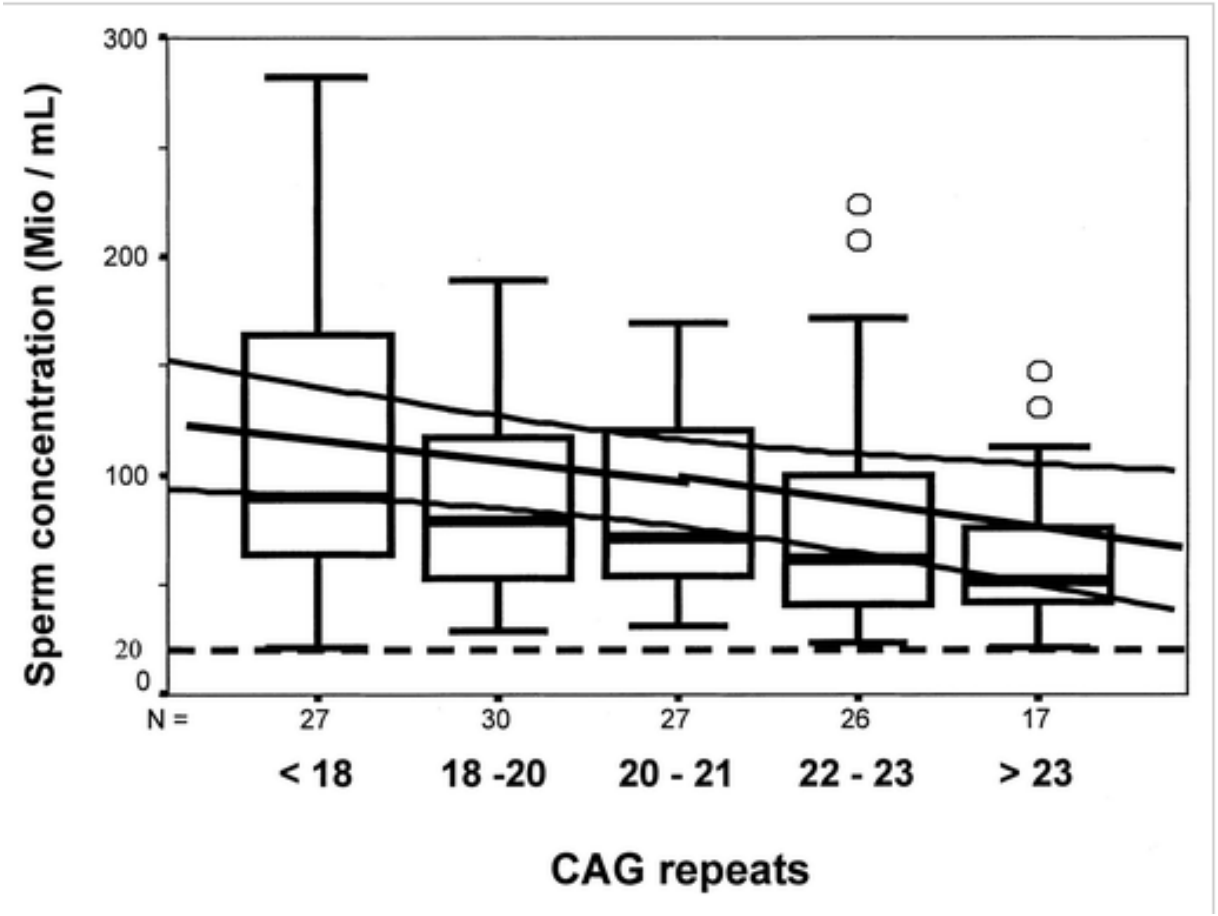
Panel B. *Hypogonadism (HG) prevalence in obese and cardiovascular disease (CVD) and obese subjects in Italy according to different testosterone thresholds.*



J Clin Endocrinol Metab. 2001 Jun;86(6):2585-90.

Inverse correlation between sperm concentration and number of androgen receptor CAG repeats in normal men.

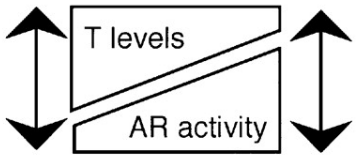
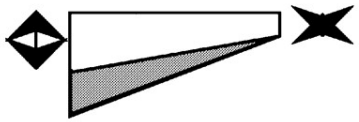
von Eckardstein S[1], Syska A, Gromoll J, Kamischke A, Simoni M, Nieschlag E.



Diabetes. 2014 Oct;63(10):3180-8. doi: 10.2337/db13-1505.

Androgen receptor roles in insulin resistance and obesity in males: the linkage of androgen-deprivation therapy to metabolic syndrome.

Yu IC[1], Lin HY[1], Sparks JD[1], Yeh S[1], Chang C[2].

	Fertile Controls	Subfertile patients
Testosterone (T)	High	Borderline-Low
SHBG	Correlates with Testosterone in both fertile and subfertile subjects	
AR CAG	Testosterone correlates with AR CAG tract length (Low T compensated by high intrinsic AR activity associated with short CAG tracts, and vice versa)	Tendency to have long AR CAG tracts (Effect of low T increased by low intrinsic AR activity associated with long CAG tracts)
Final effect on androgenicity	 High androgenicity maintained in those with low T	 Low androgenicity accentuated in those with low T
PSA and T	No correlation of PSA with T in environment of high androgenicity	PSA correlates with T in environment of low androgenicity
PSA and AR CAG length	No correlation between PSA and AR CAG tracts in environment of high androgenicity	PSA correlates with AR CAG tracts in environment of low androgenicity

J Sex Med. 2013 Oct;10(10):2518-28. doi: 10.1111/jsm.12266. Epub 2013 Jul 16.

Serum PSA as a predictor of testosterone deficiency.

Rastrelli G[1], Corona G, Vignozzi L, Maseroli E, Silverii A, Monami M, Mannucci E, Forti G, Maggi M.

Author information

Abstract

INTRODUCTION: The relationship between serum prostate-specific antigen (PSA) and testosterone (T) levels is still controversial. According to the "saturation hypothesis," a significant relationship is apparent only in the low T range.

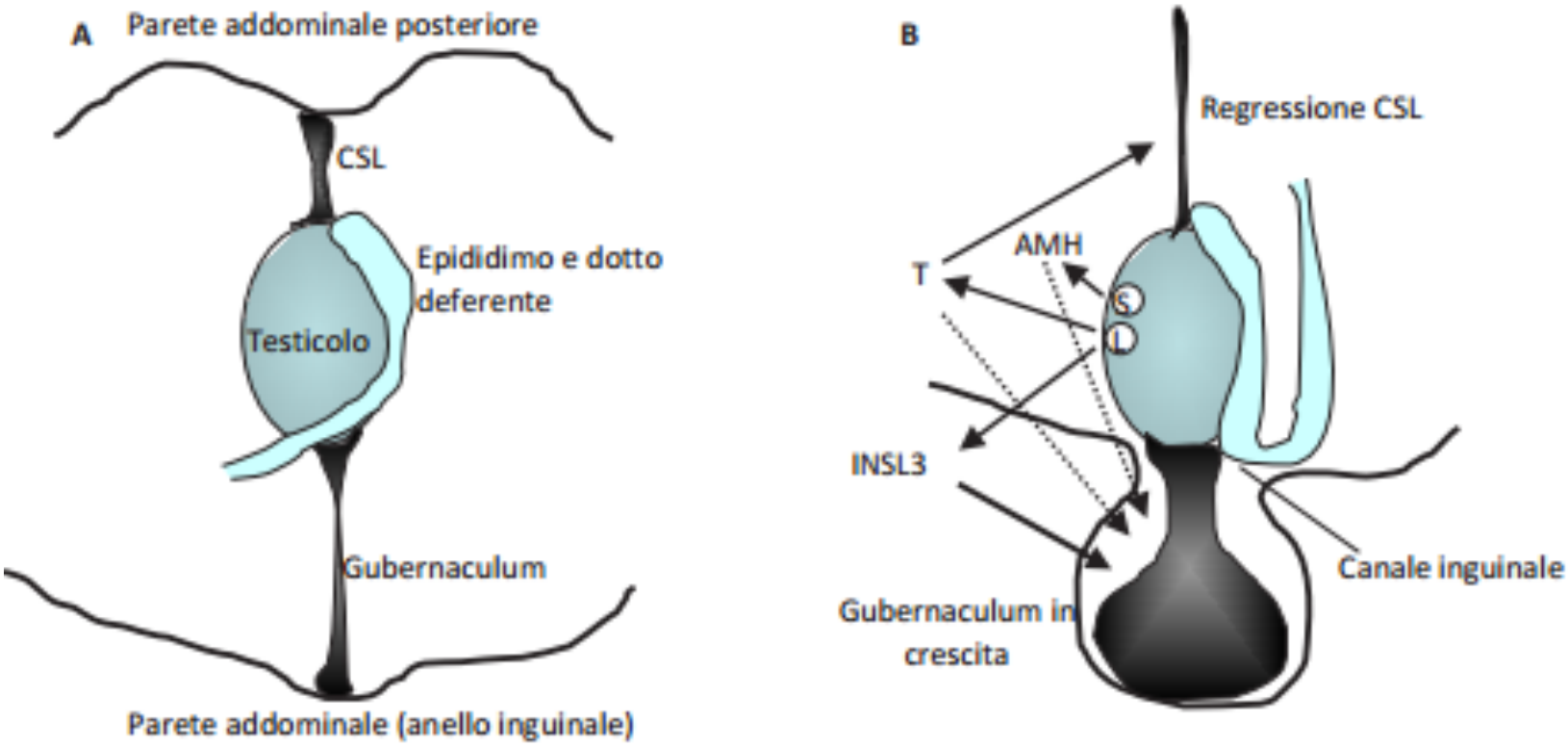
AIM: To verify whether, in a large sample of male subjects seeking medical care for sexual dysfunction (SD), PSA might represent a reliable marker of T levels.

METHODS: A consecutive series of 3,156 patients attending our unit for SD was studied. Among them, only subjects without history of prostate disease and with PSA levels<4 ng/mL (N=2,967) were analyzed.

MAIN OUTCOME MEASURES: Several hormonal and biochemical parameters were studied, along with structured interview on erectile dysfunction (SIEDY), ANDROTEST, and PsychoANDROTEST.

RESULTS: Receiver operating characteristic curve analysis for predicting severe hypogonadism (T<8 nmol/L) showed an accuracy of PSA=0.612±0.022 (P<0.0001), with the best sensitivity and specificity at PSA<0.65 ng/mL (65.2% and 55.5%, respectively). In the entire cohort, 254 subjects (8.6%) showed T<8 nmol/L and, among them, more than half (N=141, 4.8%) had PSA<0.65 ng/mL. After adjusting for age, low PSA was associated with hypogonadism-related features (i.e., delayed puberty, lower testis volume) and associated conditions, such as metabolic syndrome (hazard ratio [HR]=1.506 [1.241-1.827]; P<0.0001), type 2 diabetes (HR=2.044 [1.675-2.494]; P<0.0001), and cardiovascular diseases (HR=1.275 [1.006-1.617]; P=0.045). Furthermore, low PSA was associated with impaired sex- and sleep-related erections. The association between low PSA and hypogonadal symptoms and signs as well as with metabolic syndrome was retained even after adjusting for T levels. Sensitivity and positive predictive values of low PSA increased, whereas specificity and negative predictive value decreased as a function of age.

CONCLUSIONS: PSA is a marker of T concentrations and it may represent a new tool in confirming hypogonadism. The determination of PSA levels might give insights not only on the circulating levels of total T but also on its active fractions.



Fase trans-addominale "INSL3-dipendente"

Bay K, *et a.* Testicular descent: INSL3, testosterone, genes and the intrauterine milieu. Nat Rev Urol 2011;8:187-96.

Ferlin A, *et al.* Genetic alterations associated with cryptorchidism. JAMA 2008;300:2271-6.

Human testicular insulin-like factor 3: in relation to development, reproductive hormones and andrological disorders

Int J Andrology 2011; 34:97-109; DOI:10.1111/j.1365-2605.2010.01074.x

K. BAY AND A.M. ANDERSSON
University Department of Growth and Reproduction, Rigshospitalet, Copenhagen, Denmark
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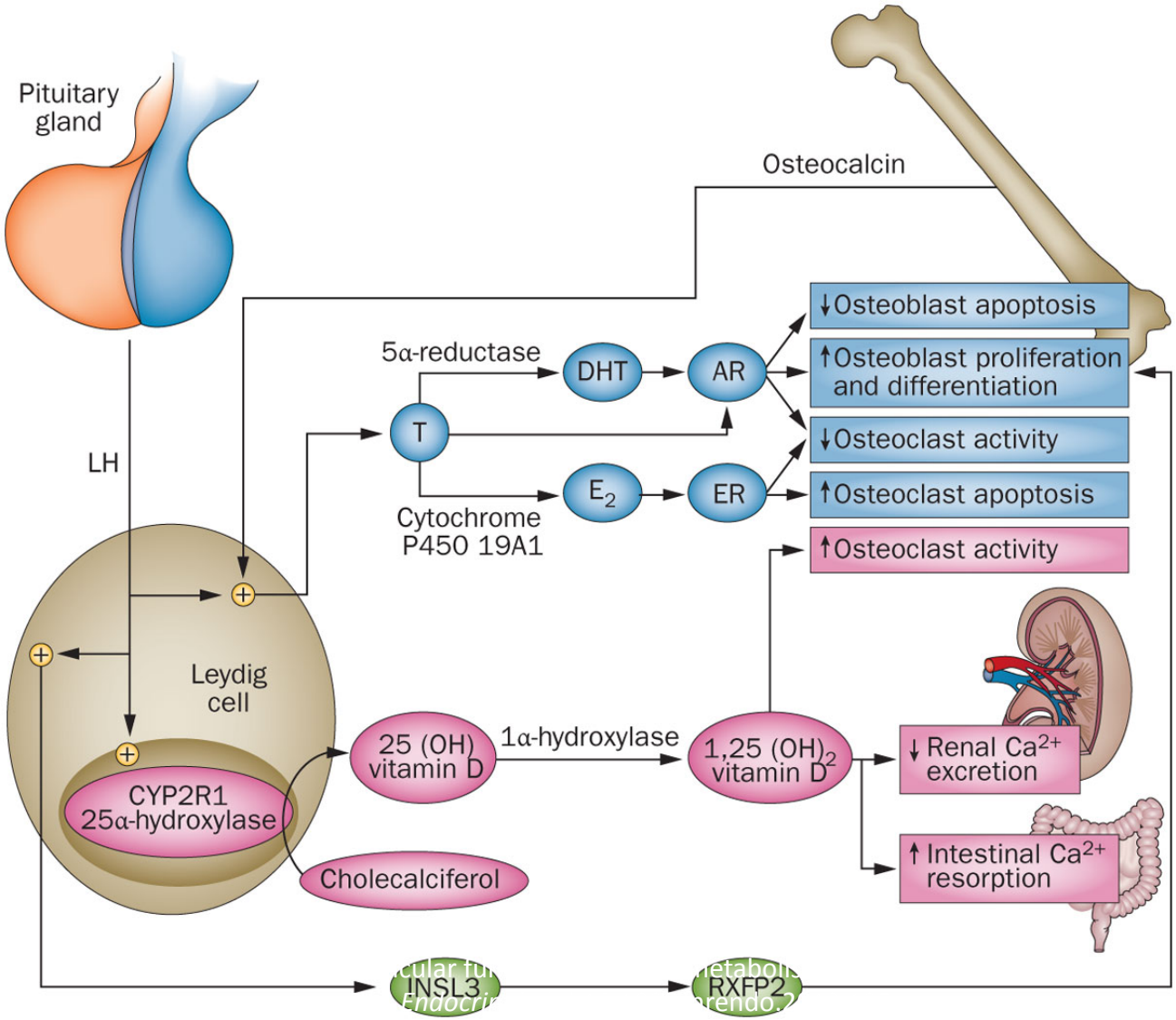
Knockout of the gene encoding insulin-like factor 3 (INSL3) results in cryptorchidism in mice due to disruption of the transabdominal phase of testicular descent. This finding was essential for understanding the complete course of testis descensus, and wound up years of speculations regarding the endocrine regulation of this process. INSL3 is, along with testosterone, a major secretory product of testicular Leydig cells. In addition to its crucial function in testicular descent, INSL3 is suggested to play a paracrine role in germ cell survival and an endocrine role in bone metabolism. INSL3 is produced in human prenatal and neonatal, and in adult Leydig cells to various extents, and is in a developmental context regulated like testosterone, with production during second trimester, an early postnatal peak and increasing secretion during puberty, resulting in high adult serum levels. INSL3 production is entirely dependent on the state of Leydig cell differentiation, and is stimulated by the long-term trophic effects mediated by luteinizing hormone (LH). Once differentiated, Leydig cells apparently express INSL3 in a constitutive manner, and the hormone is thereby insensitive to the acute, steroidogenic effects of LH, which for example is an important factor in the regulation of testosterone. Clinically, serum INSL3 levels can turn out to be a usable tool to monitor basal Leydig cell function in patients with various disorders affecting Leydig cell function. According to animal studies, foetal INSL3 production is, directly or indirectly, sensitive to oestrogenic or anti-androgenic compounds. This provides important insight into the mechanism by which maternal exposure to endocrine disrupters can result in cryptorchidism in the next generation. Conclusively, INSL3 is an interesting testicular hormone with potential clinical value as a marker for Leydig cell function. It should be considered on a par with testosterone in the evaluation of testicular function and the consequences of Leydig cell dysfunction.

L'insulin-like factor 3 testicolare umano: il suo ruolo nello sviluppo, negli ormoni della riproduzione e nei disordini andrologici

L'eliminazione del gene codificante per l'insulin-like factor 3 (INSL3) produce il criptorchidismo nei topi per alterazione della fase di discesa testicolare trans-addominale. Questa osservazione è stata essenziale per comprendere il completo processo di discesa dei testicoli e pone termine alle speculazioni relative alla regolazione endocrina di tale processo. L'INSL3 è, insieme al testosterone, il maggior prodotto della secrezione testicolare delle cellule di Leydig. Inoltre per la sua cruciale funzione nella discesa testicolare, è stato suggerito che l'INSL3 giochi un ruolo paracrino nella sopravvivenza delle cellule germinali e un ruolo endocrino nel metabolismo osseo. Nella specie umana l'INSL3 è prodotto nel periodo prenatale e neonatale e dalle cellule di Leydig dell'adulto in differenti quantità, nel contesto dello sviluppo è regolato come il testosterone con una produzione durante il secondo trimestre, un picco postnatale precoce, un aumento puberale progressivo della secrezione che dà luogo agli alti livelli serici dell'adulto. La produzione dell'INSL3 è interamente dipendente dallo stato di differenziazione delle cellule di Leydig ed è stimolata dagli effetti trofici di lungo termine mediati dall'ormone luteinizzante (LH). Una volta differenziate, le cellule di Leydig sembrano secernere l'INSL3 in modo costitutivo e pertanto l'ormone è insensibile agli effetti acuti steroidogenici del LH, che invece è per esempio un importante fattore per al regolazione del testosterone. Clinicamente i livelli serici di INSL3 possono diventare uno strumento impiegabile per monitorare la funzione basale delle cellule di Leydig nei pazienti con i disordini che coinvolgono la funzione delle cellule di Leydig. Come emerge dagli studi sugli animali, la produzione fetale di INSL3 è, direttamente o indirettamente, sensibile ai composti estrogenici o anti-androgenici. Ciò consente di entrare in modo importante nel meccanismo secondo cui l'esposizione materna ai distruttori endocrini può produrre il criptorchidismo nella generazione successiva. In conclusione, l'INSL3 è un interessante ormone testicolare con il valore clinico potenziale per marcare la funzione delle cellule di Leydig. Esso dovrebbe essere preso in considerazione, insieme al testosterone, nella valutazione della funzione testicolare e delle conseguenze della disfunzione delle cellule di Leydig.



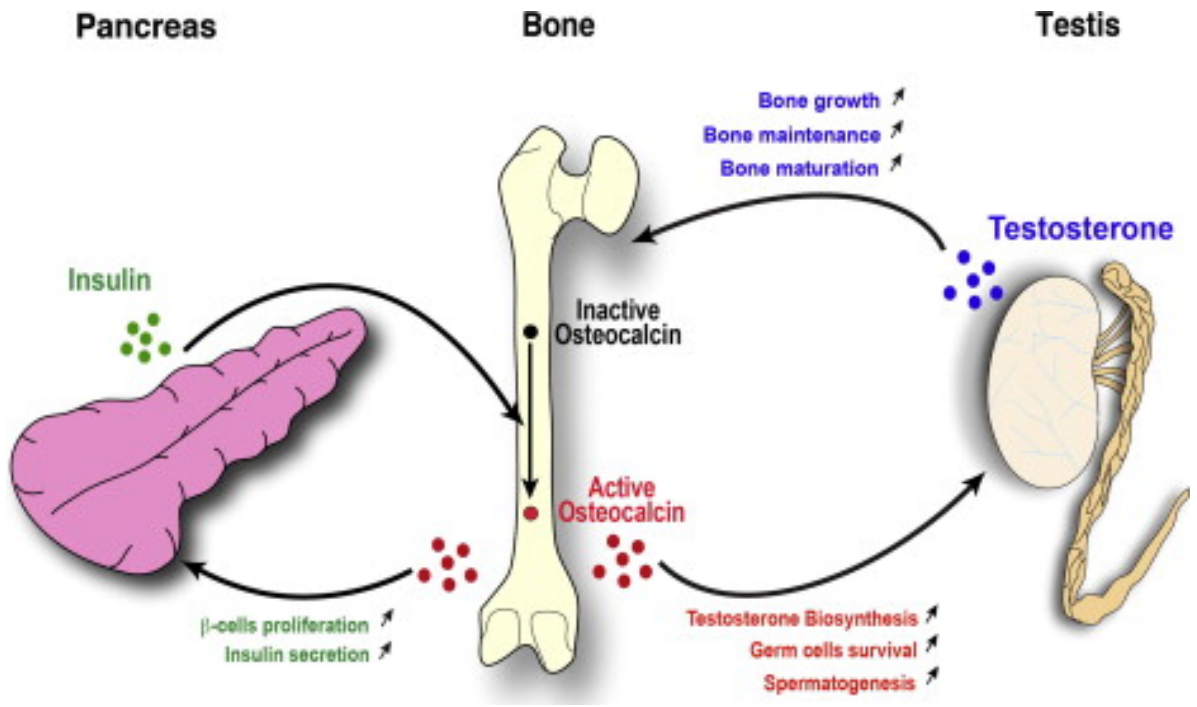


Fig. 3 Osteocalcin-stimulated testosterone biosynthesis is positively regulated by insulin signaling in osteoblasts. Insulin signaling in osteoblasts stimulates the bio-activation of osteocalcin. In a feedback loop control, undercarboxylated active osteoca...

Gerard Karsenty , Franck Oury

Regulation of male fertility by the bone-derived hormone osteocalcin

Molecular and Cellular Endocrinology, Volume 382, Issue 1, 2014, 521 - 526

http://dx.doi.org/10.1016/j.mce.2013.10.008

BJU Int. 2014 Mar 10. doi: 10.1111/bju.12732. [Epub ahead of print]

The Impact of the Androgen Deprivation Therapy on the Risk of Coronary Heart Disease in Patients with Non-Metastatic Prostate Cancer: A Population-Based Study.

Gandaglia G[1], Sun M, Popa I, Schiffmann J, Abdollah F, Trinh QD, Saad F, Graefen M, Briganti A, Montorsi F, Karakiewicz PI.

Author information

Abstract

OBJECTIVE: To examine and quantify the contemporary association between ADT and three separate endpoints: coronary artery disease (CAD), acute myocardial infarction (AMI), and sudden cardiac death (SCD), in a large United States contemporary cohort of PCa patients.

MATERIALS AND METHODS: Overall, 140,474 patients diagnosed with non-metastatic PCa between 1995 and 2009 within the Surveillance, Epidemiology, and End Results (SEER)-Medicare linked database were abstracted. Patients treated with ADT and those not receiving ADT were matched using propensity-score methodology. Ten-year CAD, AMI, and SCD rates were estimated. Competing-risks regression analyses tested the association between the type of ADT (GnRH agonists vs. bilateral orchiectomy) and CAD, AMI, and SCD, after adjusting for the risk of dying during follow-up.

RESULTS: Overall, the 10-year rates of CAD, AMI, and SCD were 25.9, 15.6, and 15.8%, respectively. After stratification according to ADT status (ADT-naïve vs. GnRH agonists vs. bilateral orchiectomy), the CAD rates were 25.1 vs. 26.9 vs. 23.2%, the AMI rates were 14.8 vs. 16.6 vs. 14.8%, and the SCD rates were 14.2 vs. 17.7 vs. 16.4%, respectively. In competing-risks multivariable regression analyses, the administration of GnRH agonists (all $P<0.001$), but not bilateral orchiectomy (all $P\geq0.7$), was associated with higher risk of CAD, AMI, and SCD.

CONCLUSIONS: The administration of GnRH agonists, but not orchiectomy, is still associated with a significantly increased risk of CAD, AMI, and, especially, SCD in patients with non-metastatic PCa. Alternative forms of ADT should be considered in patients at higher risk of CV events.

J Endocrinol Invest. 2013 May;36(5):287-92. doi: 10.3275/8514. Epub 2012 Jul 9.

Anthropometric, penile and testis measures in post-pubertal Italian males.

Foresta C[1], Garolla A, Frigo AC, Carraro U, Isidori AM, Lenzi A, Ferlin A.

Author information

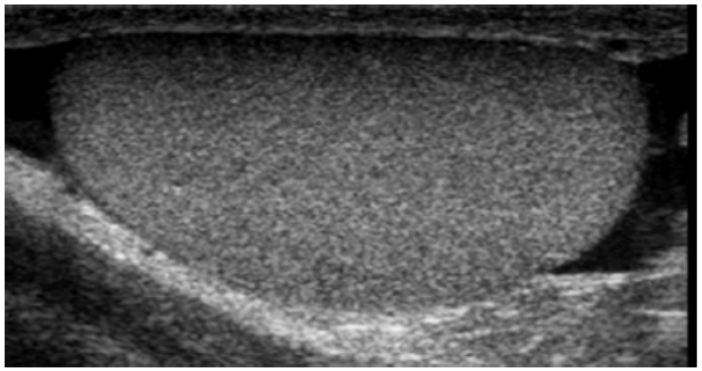
Abstract

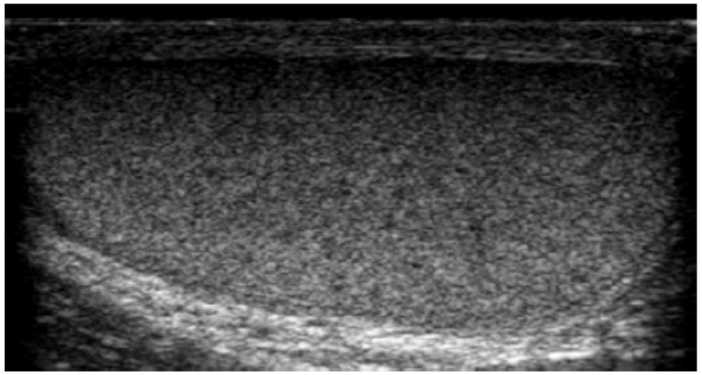
BACKGROUND: Relationships between anthropometric measures, body proportions, weight and penile dimensions in young adult males have not been previously analyzed. Furthermore, although male fertility has declined in last decades, no data on testicular volume (the best surrogate measure for spermatogenic potential) are available for the general population of young men in Italy.

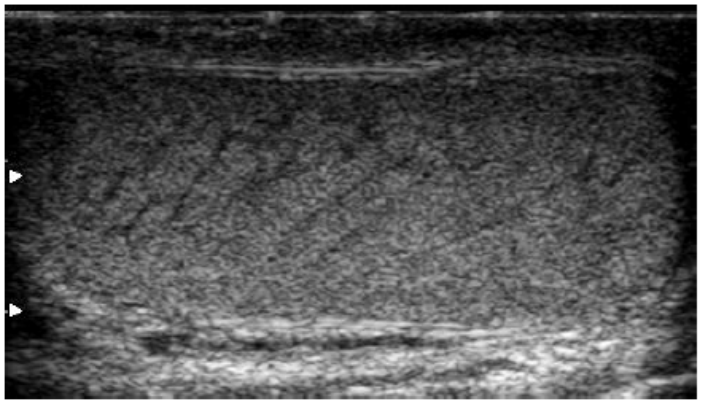
AIM: To analyze anthropometric measures and proportions, testicular volumes, and penile dimensions in a large cohort from the general population of young Italian men aged 18-19 yr. MATERIALS/SUBJECTS: We analyzed 2019 students aged 18-19 years for height, weight, body mass index (BMI), waist circumference, arm span, pubis-to-floor and crown-to-pubis length, and penile dimensions. Testicular volumes were measured by ultrasound in 776 subjects.

RESULTS: Thirty-six percent of the subjects had a pathological arm span-height difference (>3 cm) and 44.7% had a pathological pubis-to-floor/ crown-to-pubis ratio (≤ 0.92). The mean penis length was 8.9 ± 1.4 cm and the penis circumference was 9.5 ± 1.0 cm. BMI was positively associated with arm span-height difference and negatively with penis length. 23.2% of the subjects had low mean testicular volume (<12 ml).

CONCLUSIONS: The findings highlight a strong influence of BMI on skeletal proportions and penis length, identify a large proportion of subjects with testicular hypotrophy at risk for future fertility, and suggest to consider worldwide studies to redefine normal values for arm span-height difference and upper/ lower body segment ratio.







Testis homogeneity

0.Homogeneous

1.Mild
inhomogeneity
(little hypoechoic areas)

2.Moderate-severe
inhomogeneity
(hypoechoic striae)

Fig. 2

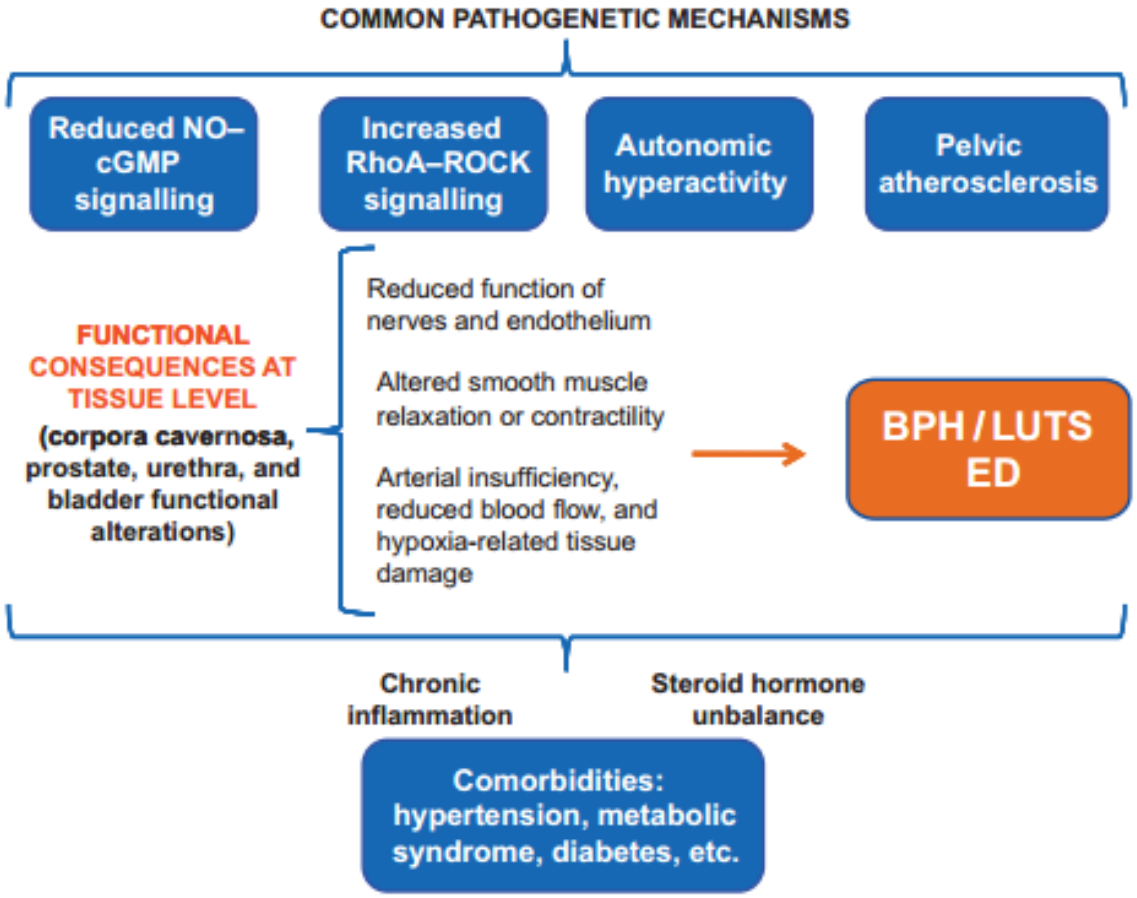
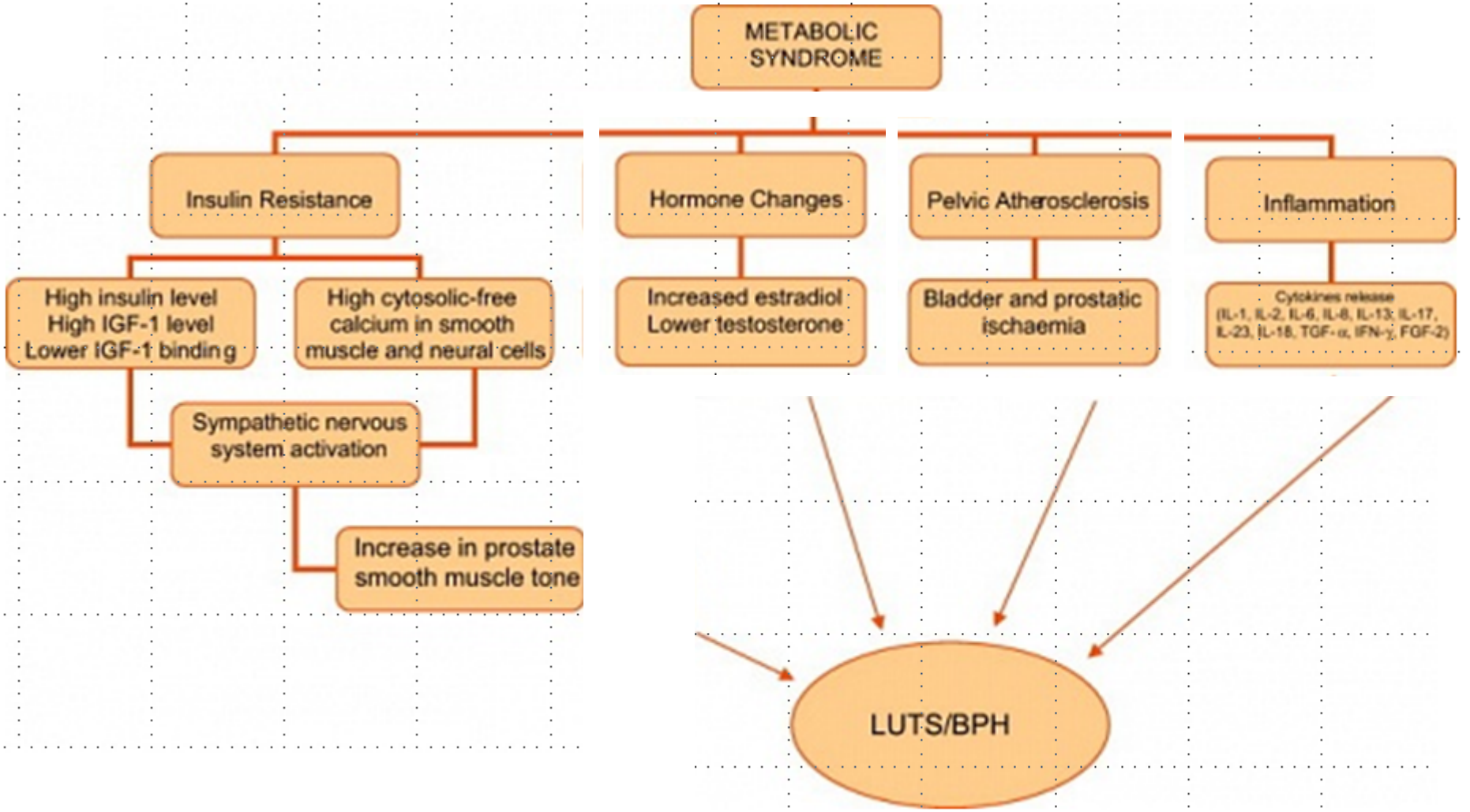


Figure 1 – Schematic representation of the common pathogenetic mechanisms linking lower urinary tract symptoms resulting from benign prostatic hyperplasia and erectile dysfunction.
NO = nitric oxide; cGMP = cyclic guanosine monophosphate; ROCK = Rho-kinase; BPH = benign prostatic hyperplasia; LUTS = lower urinary tract symptoms; ED = erectile dysfunction.

EUROPEAN UROLOGY 60 (2011) 809–825

Potential biological mechanisms for BPH/LUTS in relation to metabolic/hormonal alterations



BJU Int. 2015 Nov;116(5):791-6. doi: 10.1111/bju.13053. Epub 2015 Mar 25.

Increase of Framingham cardiovascular disease risk score is associated with severity of lower urinary tract symptoms.

Russo GI[1], Castelli T[1], Privitera S[1], Fragalà E[1], Favilla V[1], Reale G[1], Urzì D[1], La Vignera S[2], Condorelli RA[2], Calogero AE[2], Cimino S[1], Morgia G[1].

Author information

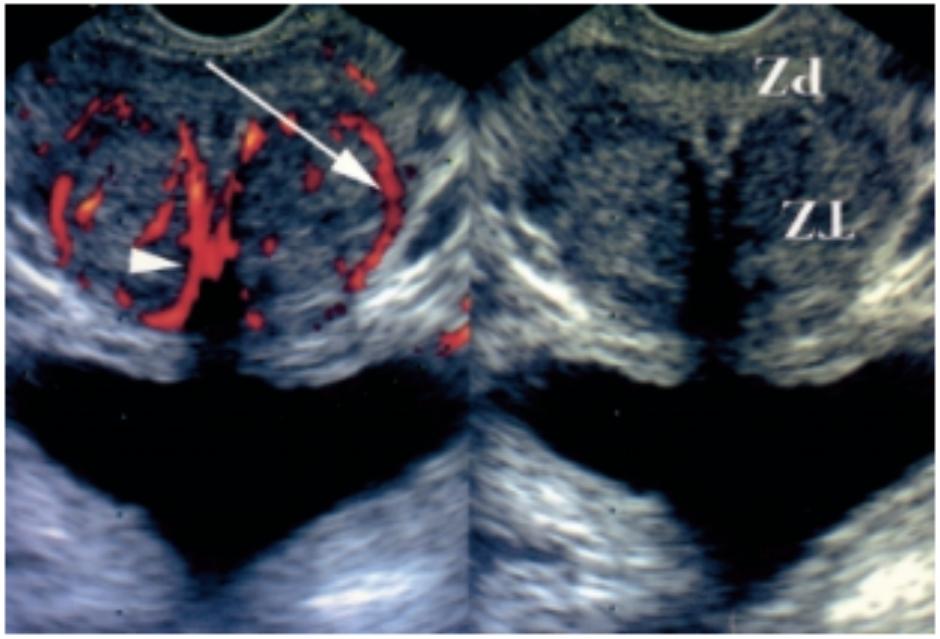
Abstract

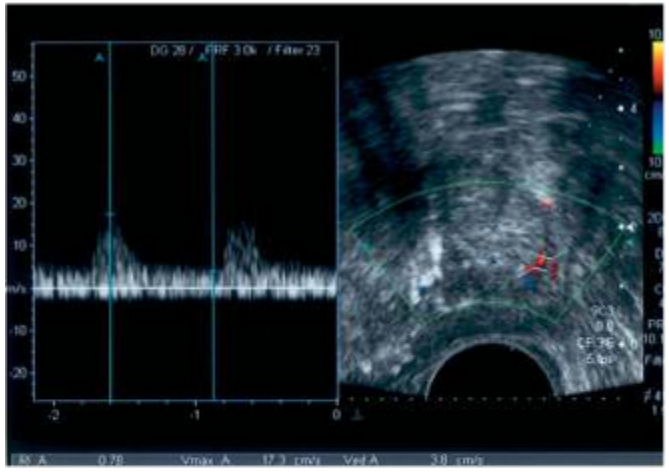
OBJECTIVE: To determine the relationship between lower urinary tract symptoms (LUTS)/benign prostatic hyperplasia (BPH) and 10-year risk of cardiovascular disease (CVD) assessed by the Framingham CVD risk score in a cohort of patients without previous episodes of stroke and/or acute myocardial infarction.

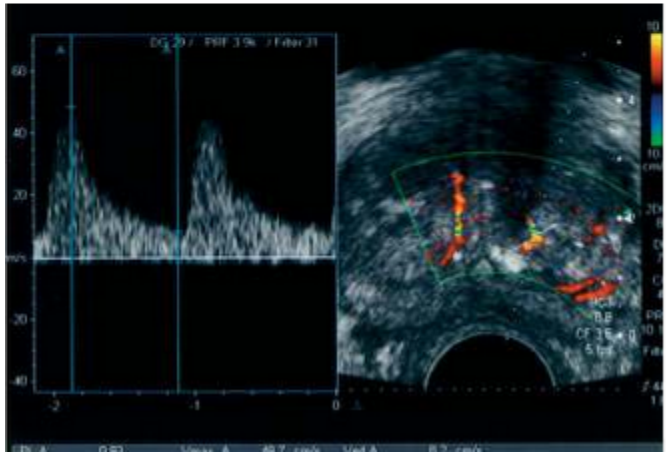
PATIENTS AND METHODS: From September 2010 to September 2014, 336 consecutive patients with BPH-related LUTS were prospectively enrolled. The general 10-year Framingham CVD risk score, expressed as percentage and assessing the risk of atherosclerotic CVD events, was calculated for each patient. Individuals with low risk had ≤10% CVD risk at 10 years, with intermediate risk 10-20% and with high risk ≥20%. Logistic regression analyses were used to identify variables for predicting a Framingham CVD risk score of ≥10% and moderate-severe LUTS (International Prostate Symptom Score [IPSS] ≥8), adjusted for confounding factors.

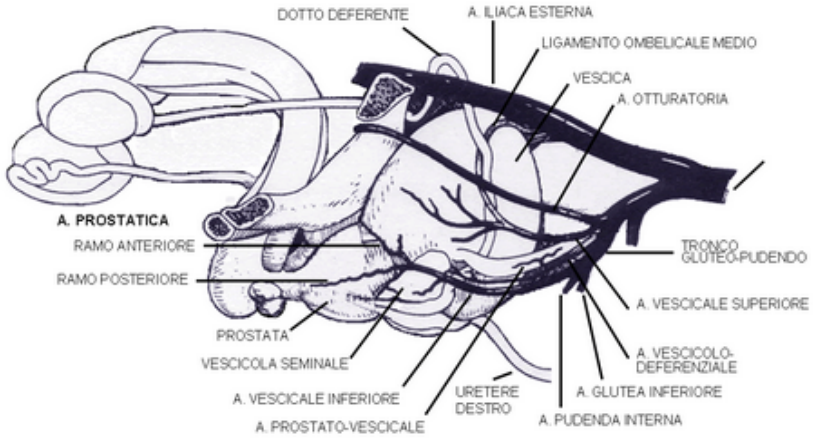
RESULTS: As category of Framingham CVD risk score increased, we observed higher IPSS (18.0 vs 18.50 vs 19.0; $P < 0.05$), high IPSS-voiding (6.0 vs 9.0 vs 9.5; $P < 0.05$) and worse sexual function. Prostate volume significantly increased in those with intermediate- vs low-risk scores (54.5 vs 44.1 mL; $P < 0.05$). Multivariate logistic regression analysis showed that intermediate- [odds ratio (OR) 8.65; $P < 0.01$) and high-risk scores (OR 1.79; $P < 0.05$) were independently associated with moderate-severe LUTS. At age-adjusted logistic regression analysis, moderate-severe LUTS was independently associated with Framingham CVD risk score of ≥10% (OR 5.91; $P < 0.05$).

CONCLUSION: Our cross-sectional study in a cohort of patients with LUTS-BPH showed an increase of more than five-fold of having a Framingham CVD risk score of ≥10% in men with moderate-severe LUTS.









Measuring Resistance Index in Patients with BPH and Lower Urinary Tract Symptoms

Huseyin Ozdemir, MD,[1] Rahmi Onur, MD,[2] Zulkif Bozgeyik, MD,[1] Irfan Orhan, MD,[2] M. Sezai Ogras, MD,[2] Erkin Ogur, MD[1]

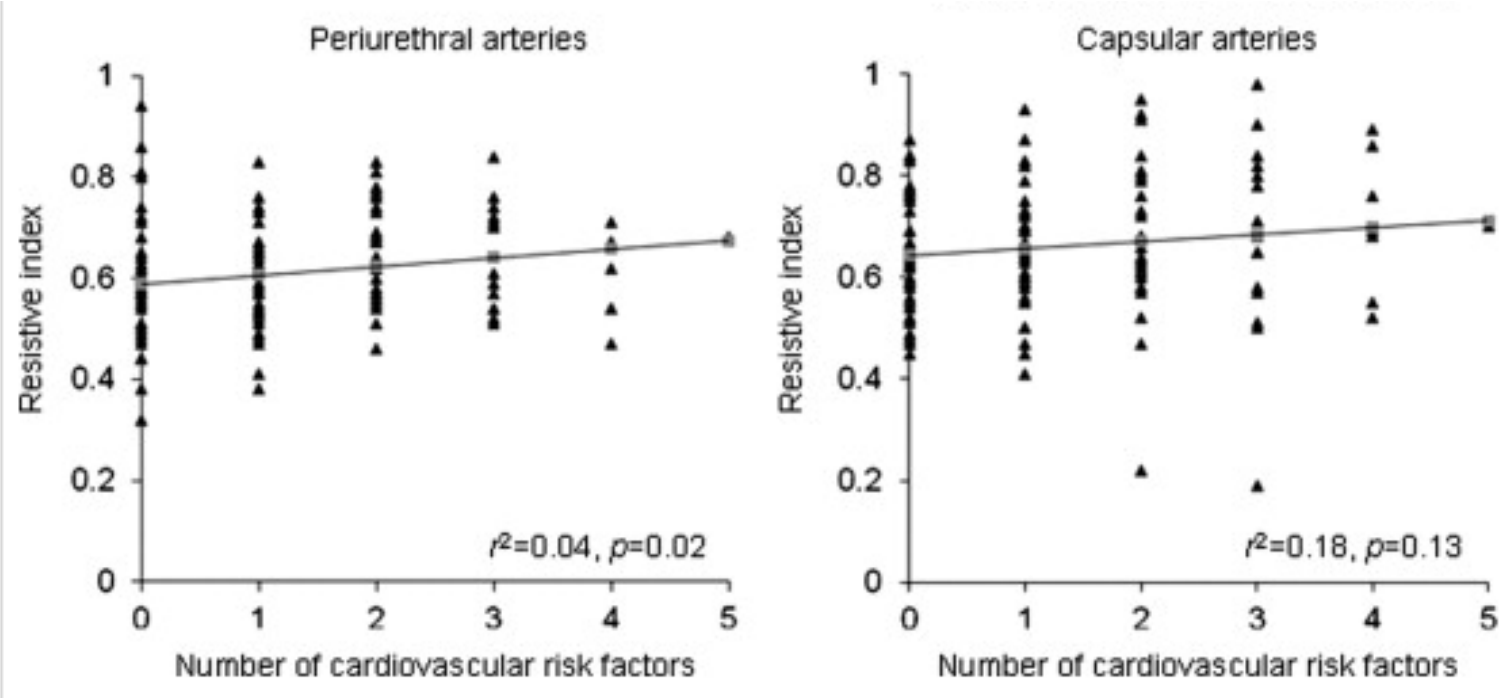
J Clin Ultrasound. 2005 May;33(4):176-80.

Comunemente dal tronco gluteopudendo dell'arteria iliaca interna deriva l'arteria prostato-vescicale che si divide nell'arteria vescicale inferiore e nell'arteria prostatica. Questa alla base della ghiandola si divide in un ramo maggiore posterolaterale ed in un ramo anteriore per la regione anterolaterale.

Urology. 2012 Feb;79(2):409-14. doi: 10.1016/j.urology.2011.09.039. Epub 2011 Dec 2.

Correlations among cardiovascular risk factors, prostate blood flow, and prostate volume in patients with clinical benign prostatic hyperplasia.

Chen IH[1], Tsai YS, Tong YC.



Ipogonadismo età adulta
Presentazioni atipiche

1. Obesità
2. Insulino resistenza
3. Sindrome metabolica
4. Storia clinica di infertilità maschile
5. Storia clinica di criptorchidismo
6. Basso PSA per età e volume prostatico
7. Osteoporosi
8. Ipovitaminosi D
9. Carcinoma della prostata in BAT
10. Basso volume testicolare
11. Riduzione ecogenicità testicolare
12. LUTS

Questioni aperte

- valenza di un singola determinazione di T
- valore clinico del decremento temporale di T
- scelte terapeutiche

A quali livelli plasmatici di T puntare?

C'è accordo sulle caratteristiche generali della terapia sostitutiva ma non sul valore di T che rappresenta l'obiettivo terapeutico

Endocrine Society sostiene che la terapia è appropriata quando il T raggiunge i livelli medio-normali nei maschi giovani e sani proponendo aggiustamenti terapeutici quando la testosteronemia è <350 ng/dl o >700 ng/dl.

- 400 ng/dl per la ripresa erezioni
- 500 ng/dl per aumentare la frequenza dei rapporti sessuali
- 600 ng/dl per aumentare il desiderio sessuale

Dal punto di vista pratico si punta ad ottenere livelli di T pari a 600 ng/dl

Caratteristiche biologiche dell'AR

Monitoraggio

- Sintomatologia a 3, 6, 12 mesi poi annualmente

- PSA prima e dopo 3, 6, 12 mesi poi annualmente
  - incrementi di PSA>1.4 ng/ml entro i 12 mesi di trattamento
  - PSA velocity>0.4 ng/ml per anno (dopo 6 mesi di trattamento e 2 anni di osservazione)
  - DRE sospetta
  - IPSS >19

- Ematocrito prima e dopo 3, 6, 12 mesi, poi annualmente
  - Se >54% interrompere la terapia , valutare ipossia e sleep apnea e poi riprendere la terapia a dosi minori

- MOC dopo 1-2 anni

A quali livelli plasmatici di T puntare?

C'è accordo sulle caratteristiche generali della terapia sostitutiva ma non sul valore di T che rappresenta l'obiettivo terapeutico

Endocrine Society sostiene che la terapia è appropriata quando il T raggiunge i livelli medio-normali nei maschi giovani e sani proponendo aggiustamenti terapeutici quando la testosteronemia è <350 ng/dl o >700 ng/dl.

- 400 ng/dl per la ripresa erezioni
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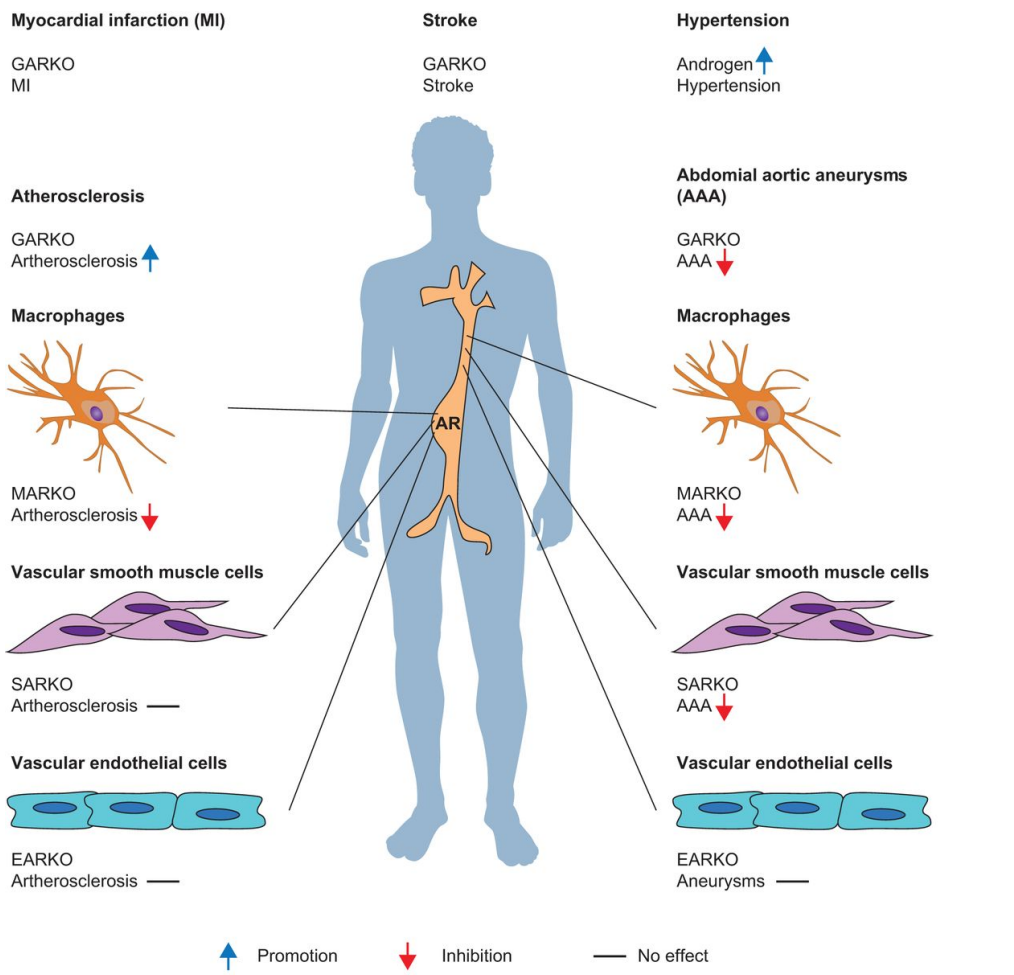
Dal punto di vista pratico si punta ad ottenere livelli di T pari a 600 ng/dl

Caratteristiche biologiche dell'AR

Figure 1 The impact of knocking out cell-specific AR on the development and progression of CVDs.



GARKO, General androgen receptor knockout; MARKO, macrophage specific androgen receptor knockout; SARKO, smooth muscle cell specific androgen receptor knockout; EARKO, endothelial cell specific androgen receptor knockout

Chiung-Kuei Huang et al. J Endocrinol 2016;229:R1-R16

Aging Male. 2016 Mar;19(1):34-9. doi: 10.3109/13685538.2015.1092021. Epub 2015 Oct 21.

Late-onset hypogonadism: the advantages of treatment with human chorionic gonadotropin rather than testosterone.

La Vignera S[1], Condorelli RA[1], Cimino L[1], Russo GI[2], Morgia G[2], Calogero AE[1].

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Table 2. Median differences from baseline to final visit among groups with intergroup analysis.

Variables	Group 1 *Gonasi*	Group 2 *Tostrex*	Group 3 *Nebid*	Group 4 *Testoviron*
Hormonal parameters				
Change from baseline of total testosterone, median (IQR)	1.2 (1.1,1.3)[b]	0.9 (0.5,1.0)[d,e]	1.6 (1.5,1.75)[a,f]	1.3 (1.3,1.45)
Change from baseline of LH, median (IQR)	−1.1 (−1.4,0.85)[a]	0.60 (−0.9,0.45)	−1.1 (−1.3,−0.95)[a]	−1.1 (−1.35,−1.0)[a]
Change from baseline of FSH, median (IQR)	−0.2 (−0.5,−0.10)	−0.2 (−0.35,−0.05)	−0.2 (−0.2,−0.10)	−0.30 (0.90,0.0)
Change from baseline of estradiol, median (IQR)	1.0 (0.0,−4.0)[a,b,c]	4.0 (1.0,−8.5)	8.0 (5.0,−10.0)	10.0 (5.5,14.5)
Change from baseline of vitamin D, median (IQR)	22.0 (17.0,25.0)[a,b,c]	4.0 (0.0,4.0)	4.0 (0.0,4.5)	3.0 (0.0,3.5)
Anthropometric and metabolic parameters				
Change from baseline of HGT, median (IQR)	−4.0 (−7.0,0.0)	−1.0 (−7.5,0.0)	0.0 (−2.0,0.0)	0.0 (−1.0,0.0)
Change from baseline of insulin, median (IQR)	−10.0 (−10.5,−1.0)	−6.0 (−8.5,−1.5)	−4.0 (−11.0,1.0)	−8.0 (−12.5,0.0)
Change from baseline of HOMA, median (IQR)	−2.3 (−2.6,0.0)	−1.3 (2.15,−0.05)	−0.8 (−.24,0.0)	−1.4 (−2.4,0.0)
Change from baseline of cholesterol, median (IQR)	−20.0 (−33.0,15.0)	−10.0 (−47.5,−7.5)	−30.0 (−40.0,−25.0)	−45.0 (−62.5,−27.5)
Change from baseline of HDL, median (IQR)	3.0 (1.5,3.5)	1.0 (0.0,−1.0)	5.50 (0.5,−7.0)	3.0 (1.0,−6.0)
Change from baseline of triglycerides, median (IQR)	−33.0 (−50.0,−15.5)	−33.0 (−38.5,−22.0)	−44.0 (−50.5,−15.0)	−50.0 (−83.0,−22.0)
Change from baseline of weight, median (IQR)	−2.0 (−4.0,−1.0)	−2.0 (−2.0,0.0)	−2.0 (−2.0,−0.5)	0.0 (−2.0,0.0)
Change from baseline of waist circumference, median (IQR)	−1.0 (−1.5,0.0)	.0 (−2.0,0.0)	−2.0 (−2.0,−0.5)	−1.0 (−3.0,0.0)
Change from baseline of loan mass, median (IQR)	3.0 (0.5,4.0)	1.0 (0.5,2.0)	1.0 (0.0,−2.5)	1.0 (0.0,2.5)
Change from baseline of fat mass, median (IQR)	−2.0 (−4.0,−2.0)	−2.0 (−2.5,−1.0)	−1.0 (−3.0,−0.5)	−1.0 (−3.0,0.0)
Sperm parameters				
Change from baseline of density, median (IQR)	1.0 (0.5,−1.5)[a,b,c]	−17.0 (−28.5,−7.0)	−22.0 (−26.5,−7.0)	−22.0 (−26.0,−6.5)
Change from baseline of progressive motility, median (IQR)	1.0 (0.0,1.0)[a,b,c]	−7.0 (−10.0,−5.0)	−13.0 (−22.0,−9.5)	−11.0 (−17.5,−5.0)
Change from baseline of normal forms, median (IQR)	1.0 (0.0,1.0)	−3.0 (−6.5,−2.0)	−4.0 (−6.5,−2.0)	−4.0 (−6.0,−2.0)
Change from baseline of ejaculate volume, median (IQR)	0.2 (0.2,0.4)	0.1 (0.1,0.15)	0.1 (0.1,0.2)	0.2 (0.1,0.2)
Change from baseline of leukocytes, median (IQR)	−0.3 (−0.5,−0.1)	0.0 (−0.55,0.0)	0.0 (−0.65,0.0)	−0.4 (−0.55,0.0)
Safety parameters				
Change from baseline of haematocrit, median (IQR)	1.0 (0.5,2.5)[a,b,c]	4.0 (1.5,4.5)[d,e]	10.0 (8.0,10.0)	8.0 (6.0,10.0)
Change from baseline of PSA, median (IQR)	0.10 (0.10,0.10)[a,b,c]	0.40 (0.20,0.40)[d,e]	0.80 (0.75,0.95)	0.70 (0.6,1.0)
Change from baseline of prostate volume, median (IQR)	5.0 (3.5,7.5)[a,b,c]	12.0 (6.5,17.0)	15.0 (5.5,19.0)	14.0 (5.0,18.5)
Questionnaires				
Change from baseline of IIEF-5, median (IQR)	4.0 (2.0,4.5)	3.0 (1.0,3.0)	2.0 (1.0,3.5)	1.0 (0.5,6.5)
Change from baseline of IPSS, median (IQR)	1.0 (0.0,2.0)	1.0 (0.0,2.0)	1.0 (0.0,2.0)	2.0 (0.0,3.0)
Change from baseline of AMS, median (IQR)	−10.0 (−11.0,−8.0)	−6.0 (−10.0,−4.5)	−9.0 (−10.0,−6.0)	−10.0 (−10.0,−6.0)

[a]$p<0.05$ versus Group 2.
[b]$p<0.05$ versus Group 3.
[c]$p<0.05$ versus Group 4.
[d]$p<0.05$ versus Group 3.
[e]$p<0.05$ versus Group 4.
[f]$p<0.05$ versus Group 4.

Grazie

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