Male Hypogonadism

Hormone Replacement Therapy – Part 2

Objectives:

1. To review the risks & benefits of testosterone therapy
2. To review alternatives to testosterone therapy
3. To review the available forms of testosterone therapy

Disclosures: none

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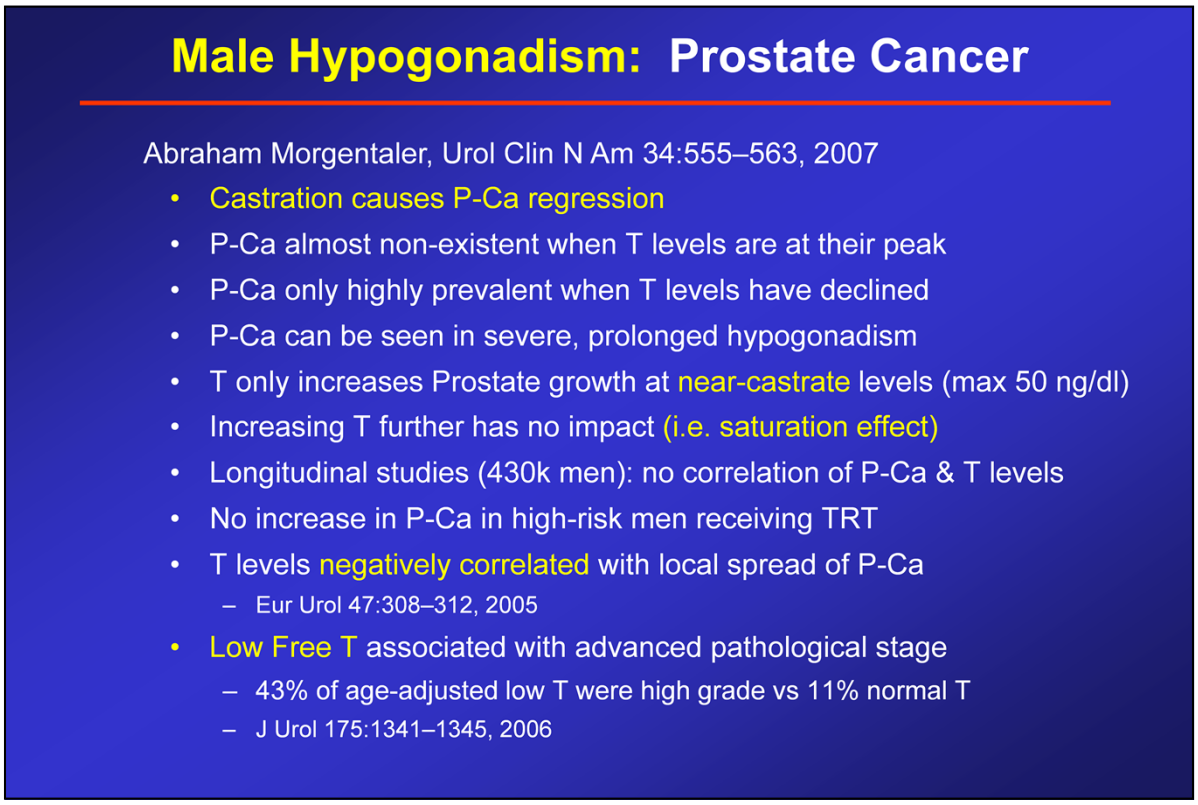
Male Hypogonadism

- Sexual Function – Libido, erectile function
- Bone Metabolism
- Muscle Mass & Strength
- Body Composition, Obesity, Insulin Resistance
- Lipoproteins
- Vascular Disease & Atherosclerosis
- Cancer: Prostate, Breast
- Neuro-psychological
- Erythropoiesis
- Skin



The long-standing concern that testosterone replacement therapy (TRT) may increase the risk of prostate cancer (PCa) has come under new scrutiny. Arguments used to support this concern lack a scientific basis. The original assertion by Huggins that administration of testosterone (T) caused "enhanced growth" of PCa was based on only a single patient. New evidence suggests that TRT has little, if any, negative impact on the prostate, even in men with a history of PCa. A saturation model is proposed that is consistent with regression of cancer when T is reduced to castrate levels and with lack of observed growth when serum T is increased.

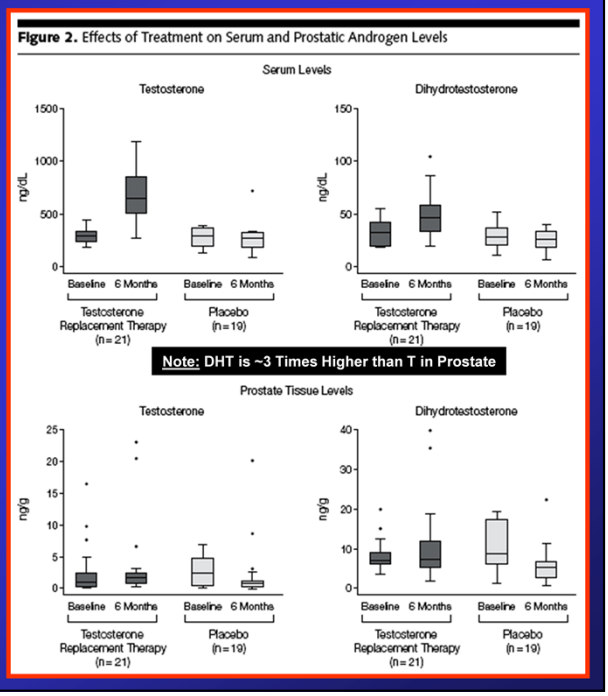
Male Hypogonadism: Prostate Cancer

Effect of Testosterone Replacement Therapy on Prostate Tissue in Men With Late-Onset Hypogonadism
A Randomized Controlled Trial
JAMA 296:2351-2361, 2006
Marks LS, Mazer NA, Mostaghel E, et al.

Biweekly testosterone enanthate 150 mg
Estradiol 22 → 37
PSA 0.90 → 0.74
No change: SHBG, gene expression

Table 1. Baseline Characteristics*

	Testosterone Replacement Therapy (n = 21)	Placebo (n = 19)	*P* Value†
Age, y	68 (44-78)	70 (45-78)	.47
Body mass index‡	28.34 (22.70-37.90)	29.57 (23.60-37.80)	.58
Testosterone level, ng/dL	221 (163-320)	252 (144-328)	.22
Prostate-specific antigen, ng/mL	1.55 (0.27-5.78)	0.97 (0-2.47)	.02
Prostate volume, mL§	43.75 (15.50-112.00)	36.75 (17.20-105.00)	.36
Transition zone volume, mL§	20.99 (4.76-76.50)	18.38 (6.44-54.00)	.57
International Prostate Symptom Score (voiding symptoms)	13 (0-26)	12 (0-27)	.47



Context Prostate safety is a primary concern when aging men receive testosterone replacement therapy (TRT), but little information is available regarding the effects of TRT on prostate tissue in men.

Objective To determine the effects of TRT on prostate tissue of aging men with low serum testosterone levels.

Design, Setting, and Participants Randomized, double-blind, placebo controlled trial of 44 men, aged 44 to 78 years, with screening serum testosterone levels lower than 300 ng/dL (10.4 nmol/L) and related symptoms, conducted at a US community-based research center between February 2003 and November 2004.

Intervention Participants were randomly assigned to receive 150 mg of testosterone enanthate or matching placebo intramuscularly every 2 weeks for 6 months.

Main Outcome Measures The primary outcome measure was the 6-month change in prostate tissue androgen levels (testosterone and dihydrotestosterone). Secondary outcome measures included 6-month changes in prostate-related clinical features, histology, biomarkers, and epithelial cell gene expression.

Results Of the 44 men randomized, 40 had prostate biopsies performed both at baseline and at 6 months and qualified for per-protocol analysis (TRT, n=21; placebo, n=19). Testosterone replacement therapy increased serum testosterone levels to the midnormal range (median at baseline, 282 ng/dL [9.8 nmol/L]; median at 6 months, 640 ng/dL [22.2 nmol/L]) with no significant change in serum testosterone levels in matched, placebo-treated men. However, median prostate tissue levels of testosterone (0.91 ng/g) and dihydrotestosterone (6.79 ng/g) did not change significantly in the TRT group. No treatment-related change was observed in prostate histology, tissue biomarkers (androgen receptor, Ki-67, CD34), gene expression (including *AR*, *PSA*, *PAP2A*, *VEGF*, *NXK3*, *CLU* [*Clusterin*]), or cancer incidence or severity. Treatment-related changes in prostate volume, serum prostate-specific antigen, voiding symptoms, and urinary flow were minor.

Conclusions These preliminary data suggest that in aging men with late-onset hypogonadism, 6 months of TRT normalizes serum androgen levels but appears to have little effect on prostate tissue androgen levels and cellular functions. Establishment of prostate safety for large populations of older men undergoing longer duration of TRT requires further study.

Pretreatment Serum Testosterone Level as a Predictive Factor of Pathological Stage in Localized Prostate Cancer Patients Treated with Radical Prostatectomy

Imamoto T et al: European Urology 47:308–312, 2005

82 pts - clinically localized prostate cancer → radical prostatectomy

Pathological Gleason score	
≤4	4 (4.9)
5–6	37 (45.1)
7	34 (41.5)
8–10	7 (8.5)
Pathological stage	
pT2a	36 (43.9)
pT2b	22 (26.8)
pT3a	14 (17.1)
pT3b	9 (11.0)
pT4	1 (1.2)

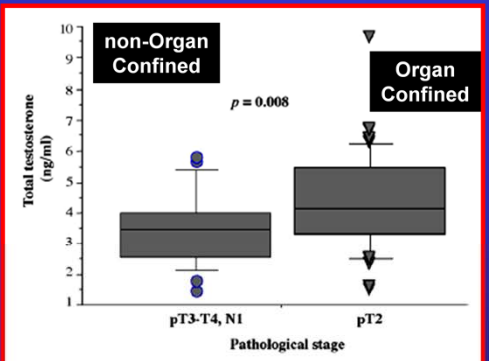


Fig. 1. Nonparametric univariate analysis of relationship between pretreatment T and pathological stage.

Table 4
Multivariate analysis of significant predictors of extraprostatic disease (pT2 versus pT3–T4, N1) according to the Cox regression model

Variable	Relative hazards ratio	95% confidence interval	*p*-value
PSA (ng/ml) (≤10/>10)	0.191	0.056–0.650	0.0081
Pathological Gleason score (2–6/7–10)	0.125	0.033–0.478	0.0024
Total testosterone (ng/ml)	2.167	1.291–3.637	0.0034

Objective: Pretreatment serum level of testosterone (T) is a potential prognostic factor for prostate cancer. The present study was conducted to evaluate the clinical significance of pretreatment serum T level in patients with clinically localized prostate cancer.

Materials and Methods: The subjects were 82 clinically localized prostate cancer patients treated with radical prostatectomy, whose pretreatment T levels were recorded. We investigated clinical and pathological factors such as pretreatment serum T level, age, pretreatment PSA or pathological Gleason score concerning the association with pathological stage and biochemical recurrence.

Results: The mean pretreatment T level was significantly lower in patients with non-organ-confined prostate cancer (pT3–T4, N1; 3.44 1.19 ng/ml) than in patients with organ-confined cancer (pT2; 4.33 1.42 ng/ml) (p = 0.0078). Multivariate analysis demonstrated that pathological Gleason score, pretreatment serum T level and pretreatment PSA were significant predictors of extra-prostatic disease. When the patients were divided into high and low T level groups according to the median value, pretreatment T levels were not significantly associated with PSA recurrence rates (p = 0.7973).

Conclusions: A lower pretreatment T level appears to be predictive of extra-prostatic disease in patients with localized prostate cancer.

Absence of Relationship Between Steroid Hormone Levels & Prostate Cancer Tumor Grade

Sher DJ et al; Oncology 73: 356–361, 2009

Table 4. Multivariate analysis of predictors of Gleason score >6 on prostate biopsy and at radical prostatectomy

	Gleason Score at Biopsy			Gleason Score at Radical Prostatectomy		
Covariate	n*	OR (95% CI)	*P* Value	n*	OR (95% CI)	*P* Value
		Testosterone				
Testosterone (ng/dL)	539		.71	199		
Q1 <338		1 (referent)			1 (referent)	.50
Q2 >338 but <440		0.83 (0.51,1.34)			1.35 (0.53,3.41)	
Q3 >440 but <579		0.75 (0.46,1.22)			0.83 (0.35,1.97)	
Q4 >579		0.88 (0.53,1.44)			0.71 (0.30,1.68)	
SHBG (nmol/L)†		1.00 (0.99,1.01)	.37		1.00 (0.99,1.02)	.71
Testosterone (ng/dL)	505		.74	179		.66
Q1 <338		1 (referent)			1 (referent)	
Q2 >338 but <440		0.88 (0.53,1.47)			1.48 (0.56,3.93)	
Q3 >440 but <579		0.88 (0.53,1.47)			0.90 (0.35,2.24)	
Q4 >579		1.14 (0.66,1.95)			0.87 (0.34,2.22)	
SHBG (nmol/L)†		1.00 (0.99,1.01)	.69		1.00 (0.99,1.02)	.92
BMI (kg/m^2)			.11			.31
<25		1 (referent)			1 (referent)	
≥25 but <30		1.39 (0.83,2.32)			0.95 (0.42,2.16)	
≥30		1.88 (1.04,3.38)			1.74 (0.64,4.71)	
Age (y) at diagnosis†		1.04 (1.01,1.06)	<.01		1.00 (0.96,1.05)	.90
PSA (ng/dL) at diagnosis†		1.06 (1.02,1.09)	<.01		1.20 (1.04,1.38)	.01

OBJECTIVES To analyze the relationship between plasma testosterone and estradiol levels on prostate biopsy and radical prostatectomy Gleason scores in a cohort of patients with newly diagnosed prostate cancer.

METHODS Patients with prostate cancer evaluated at the Dana-Farber Cancer Institute from 2001 to 2005 who were enrolled in a prospective sample banking protocol were eligible for this study. Stored plasma was processed for total testosterone, total estradiol, and sex hormone-binding globulin levels using enzyme-linked immunosorbent assays. The frequency of high-grade biopsy and radical prostatectomy Gleason scores (6) was the primary endpoint. Univariate and multivariate logistic regression analyses were performed to determine the relationship between the hormone levels and high-grade Gleason scores while adjusting for sex hormone-binding globulin, age, body mass index, and prostate-specific antigen.

RESULTS A total of 539 patients were included in this study, 199 of whom underwent radical prostatectomy. The median prostate-specific antigen level was 5.1 ng/dL, and 67% of the cancers were not palpable. The Gleason score was 2-6, 7, and 8-10 in 53%, 37%, and 10% of the cancers, respectively. On univariate analysis of the high-grade biopsy and radical prostatectomy Gleason score, the total testosterone, total estradiol, and estradiol-to-testosterone ratio were not significant

as continuous or categorical variables. Adjusting these results for sex hormone-binding globulin level, body mass index, age, and prostate-specific antigen level did not change the conclusions, and these results were unchanged when categorizing high-grade prostate cancer as Gleason score 8-10.

CONCLUSIONS No relationship was found between the circulating steroid hormone levels and the Gleason score in this cohort.

Table 4 The results of the multivariate analyses are listed in Table 4. Adjusting only for SHBG estimated the relationship among free testosterone, estradiol, and Gleason score, and we found no significant associations. No significant relationships were found between the hormone levels and prostate biopsy or radical prostatectomy Gleason score after adjustment for SHBG, BMI, age, and PSA level. These results were unchanged when the hormones were treated as continuous variables (data not shown). In addition, testosterone, estradiol, and the estradiol-to-testosterone ratio were not significant covariates when all were placed in the same model. For all 3 adjusted analyses, age and PSA remained significantly associated with a greater biopsy Gleason score. In contrast, an increasing BMI was borderline significantly related to a greater Gleason score.

UROLOGY 73: 356–361, 2009.

Serum testosterone is associated with aggressive prostate cancer in older men: results from the Baltimore Longitudinal Study of Aging

Pierorazio PM et al; BJUI 105, 824–829, 2010

TABLE 1 The characteristics of the men at the initial visit

Median (range), mean (SD) variable	All men	Others*	High-risk	P
No. of men	781	745	36	
Age, years	51.4 (22.5, 90)	50.7 (22.5, 90)	58.4 (43.2, 86)	
	51.6 (15.2)	51.2 (15.2)	60.3 (11)	<0.001
Height, cm	176.8 (157.7, 197.6)	176.8 (157.7, 197.6)	176.5 (158.5, 192.4)	
	177 (6.7)	177.1 (6.7)	176.2 (6.3)	0.42
Weight, kg	79 (53.3, 152)	79.0 (53.3, 152.1)	76.9 (64.8, 105.5)	
	80.5 (12.5)	80.6 (12.6)	77.6 (9)	0.06
Number of visits	4 (1, 8)	4 (1, 8)	4 (1, 7)	
	3.7 (1.8)	3.7 (1.8)	3.8 (1.7)	0.64
Time between visits, years	2.6 (0.9, 18.3)	2.6 (0.9, 18.3)	3.6 (0.9, 11.5)	
	4 (2.9)	4 (2.9)	4.1 (2.6)	0.82
Total testosterone, ng/dL /28.8 = nmol/L	450.9 (72.3, 856.9)	451.2 (72.3, 856.9)	435.2 (134.1, 726.3)	
	460.4 (116.1)	461.4 (115.6)	440.3 (127.1)	0.29
FTI (TT/SHBG)	0.24 (–0.05, 0.75)	0.24 (–0.05, 0.75)	–	
	0.25 (0.12)	0.25 (0.12)	0.20 (0.09)	0.083
SHBG, nmol/L All Unusually High	78.3 (18.73, 229.7)	78.5 (18.73, 229.7)	72.7 (33.41, 150.8)	
	81.97 (26.5)	82.08 (26.4)	79.68 (28.0)	0.06
DHEAS, ng/mL	1630 (112, 6666)	1670 (112, 6666)	1330 (367, 4720)	
	1828.3 (1108)	1846.3 (1108.8)	1473.47 1045)	0.063
Free testosterone, ng/dL	5.05 (0.62, 13.52)	5.05 (0.62, 13.52)	4.84 (1.59, 8.745) All Low	
	5.21 (1.74)	5.22 (1.75)	5.02 (1.63)	0.52

*Includes non-cancers and cancers defined as not high-risk.

OBJECTIVE To evaluate the relationship between testosterone levels and the development of high-risk prostate cancer, by prospectively examining serum androgen concentrations in a well-studied cohort, as the role of testosterone in prostate cancer progression is debated.

PATIENTS AND METHODS The study comprised 781 men in the Baltimore Longitudinal Study of Aging who had sex steroid measurements before a diagnosis of prostate cancer, or at their last visit for those without cancer (no cancer, 636; cancer, not high risk, 109; cancer, high risk, 36). High-risk cancer was defined as death from prostate cancer, a prostate specific antigen (PSA) level of ≥20 ng/mL at diagnosis, or a Gleason score of ≥8. The hazard ratio (HR) of high-risk disease was determined using a Cox proportional hazards regression model with simple updating, and risk rates were stratified by age and tercile for androgens of interest based on the proportional hazards analyses.

RESULTS The likelihood of high-risk prostate cancer doubled per unit (0.1) increase in the free testosterone index (FTI) for patients aged >65 years (HR 2.07, 95% confidence interval, CI, 1.01–4.23; *P*=0.047); the likelihood for men aged ≤65 years was inversely related to the FTI (HR 0.96, 95% CI 0.35–2.6; *P*=0.9). The risk rate per person-years increased from lowest to highest tercile of FTI for the oldest men (age >70 years) but this trend was not apparent among younger men.

CONCLUSION Higher levels of serum free testosterone are associated with an increased risk of aggressive prostate cancer among older men. These data highlight the importance of prospective trials to insure the safety of testosterone-replacement therapy.

Serum testosterone is associated with aggressive prostate cancer in older men: results from the Baltimore Longitudinal Study of Aging

Pierorazio PM et al; BJUI 105, 824–829, 2010

High-Risk Disease Cancer defined:
- Death from disease
- PSA >20 ng/mL
- Gleason Score ≥8

"Other" – non High Risk Cancer??

Risk Rate: number of events/total follow-up time for all subjects, multiplied by 100,000

Rates per 10 person-years:
0.07 → 0.09 → 0.12

Therefore, if you are >70 yo w/ low free testo but your TT/SHBG is > other 70 yo's, then your chance of developing a "high risk" cancer increases from 7% to 12% in the next 10 years (based on data from 22 cancers)

TABLE 2 Patients with high-risk prostate cancer (events) per person-years by tercile of FTI

(TT/SHBG)	Age group, years		
FTI tercile	≤60	60–70	>70
I			
Events/person-years*	760	730	679
N events **18**	7	7	4
N other	172	116	83
II			
Events/person-years	494	884	864
N events **24**	7	10	7
N other	171	112	81
III			
Events/person-years	590	684	1166
N events **27**	7	9	11
N other	176	117	81

Total Events: 69 ?

**Rates per 100 000 person-years.*

Low pretreatment serum total testosterone is associated with a high incidence of Gleason score 8 – 10 disease in prostatectomy specimens: data from ethnic Chinese patients with localized prostate cancer Dai B et al: BJUI 110:E667-E672, 2012

110 patients - clinically localized prostate cancer → radical prostatectomy

Variables	Threshold 1 (Hypogonadism: total testosterone <300 ng/dL)			Threshold 2 (Hypogonadism: total testosterone <250 ng/dL)		
	Hypogonadism	Eugonadism	*P*	Hypogonadism	Eugonadism	*P*
No. of patients	35	75		18	92	
Mean (range) age, years	65.8 (49–77)	66.4 (56–78)	0.618	65.7 (49–77)	66.3 (52–78)	0.721
Mean (range) BMI, kg/m^2	23.8 (15.6–29.4)	23.3 (15.6–32.3)	0.562	24.2 (15.6–32.3)	23.1 (15.6–28.7)	0.041
Mean (range) PSA, ng/mL	26.8 (2.0–169.1)	17.5 (1.4–122.1)	0.221	17.1 (1.4–66.4)	20.3 (2.0–169.1)	0.662
Pathological Gleason score, *n* (%)						
<8	25 (71.4)	63 (84.0)	0.125	10 (55.6)	78 (84.8)	0.005
≥8	10 (28.6)	12 (16.0)		8 (44.4)	14 (15.2)	
Pathological stage, *n* (%)						
T2a–T2c	19 (54.3)	50 (66.7)	0.211	10 (55.6)	59 (64.1)	0.491
T3a–T3b	16 (45.7)	25 (33.3)		8 (44.4)	33 (35.9)	

OBJECTIVE • To investigate the relationship between preoperative serum total testosterone level and prognostic factors of Chinese patients with clinically localized prostate cancer (PCa).

PATIENTS AND METHODS • A total of 110 patients with localized PCa, treated by radical prostatectomy (RP), were included in this prospective study.

• Clinical and pathological data from each patient were collected. Total testosterone was measured on the morning of surgery.

• Total testosterone levels for each patient were compared using two thresholds: threshold 1 (total testosterone < 300 ng/dL vs total testosterone ≥ 300 ng/dL) and threshold 2 (total testosterone < 250 ng/dL vs total testosterone ≥ 250 ng/dL).

RESULTS • The median preoperative total testosterone level was 346 ng/dL. Gleason scores of ≤ 6, 7 and ≥ 8 were found in the RP specimens from 21 (19.1%), 67 (60.9%) and 22 (20.0%) patients, respectively.

• Compared with those with low grade disease, patients with high grade disease (Gleason score ≥ 8) in RP specimens had a significantly lower preoperative total testosterone.

• When comparing 35 patients with hypogonadism with 75 patients with eugonadism, classified by threshold 1, no significant relationships were found.

• When comparing 18 patients with hypogonadism with 92 patients with eugonadism, classified by threshold 2, pathological Gleason score ≥ 8 tumours were more common in patients with hypogonadism.

CONCLUSION • Setting the threshold for hypogonadism at the level of pretreatment serum total testosterone < 250 ng/dL is appropriate for ethnic Chinese patients with localized PCa, because patients with pretreatment total testosterone < 250 ng/dL are associated with a higher incidence of Gleason score 8 – 10 disease in RP specimens.

Male Hypogonadism: Prostate Cancer

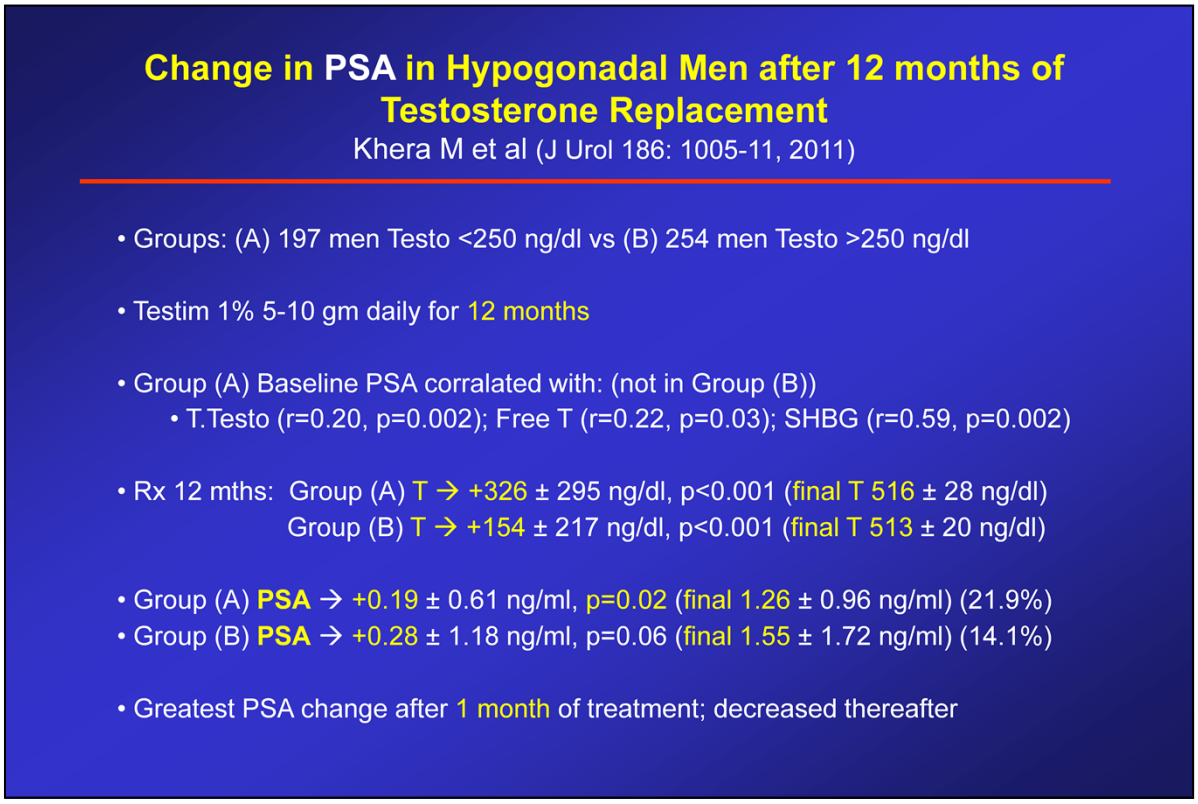
Low Pre-treatment Testosterone Predicts Poor Prognostic Factors
in Patients with Localized Prostate Cancer

TABLE 4 Summary of studies supporting correlations between low pretreatment total testosterone and poor prognostic factors in patients with localized PCa

Author	Country where study conducted	Samples	Threshold for low pretreatment total testosterone (ng/dL)	Patients with low pretreatment total testosterone (%)	Pretreatment total testosterone level (ng/dL)			Correlated prognostic factors
					Mean	Median	Range	
Present study	Chinese	110	<250	16.4	393	346	46–966	Higher Gleason score
Lane *et al.* [9]	American	455	<220	5.5	NA	395	316–507 (interquartile)	Higher Gleason score
Teloken *et al.* [8]	Brazil	64	<270	35.9	362	NA	NA	Higher positive surgical margin rate
Salonia *et al.* [17]	Italian	673	<300	21.4	450	450	2–1360	Higher Gleason score and advanced stage
Botto *et al.* [7]	French	431	<300	14.4	NA	440	90–1580	Higher Gleason score
Yamamoto *et al.* [18]	Japanese	272	<300	18.0	NA	401	149–943	Higher biochemical failure rate
Isom-Batz *et al.* [12]	American	326	<300	25.0	NA	385	133–998	Higher Gleason score
Xylinas *et al.* [10]	French	107	<300	19.6	NA	NA	NA	Higher Gleason score and advanced stage
Roder *et al.* [19]	Danish	227	<317	28.1	NA	403	63–1153	Higher biochemical failure rate
Imamoto *et al.* [11]	Japanese	82	<387	50.0	NA	387	146–943	Advanced stage

Dai B et al: BJUI 110:E667-E672, 2012

Table 4 has a summary of the present data and recently published studies that support correlations between low pretreatment total testosterone and poor prognostic factors in patients with localized PCa treated by RP. It should be noted that the definition of low pretreatment total testosterone varied among these studies, although 300 ng/dL was the most commonly used threshold.



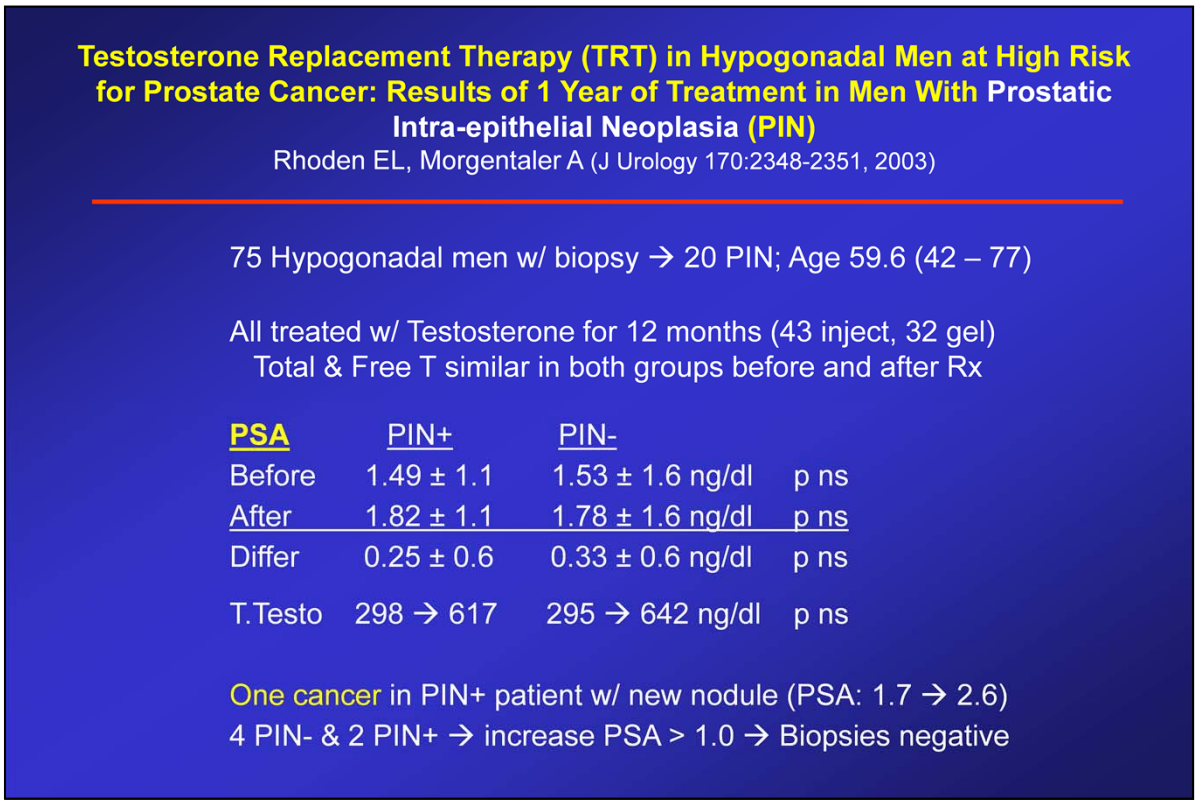
PURPOSE: We measured prostate specific antigen after 12 months of testosterone replacement therapy in hypogonadal men.

MATERIALS AND METHODS: Data were collected from the TRiUS (Testim® Registry in the United States), an observational registry of hypogonadal men on testosterone replacement therapy (849). Participants were Testim naïve, had no prostate cancer and received 5 to 10 gm Testim 1% (testosterone gel) daily.

RESULTS: A total of 451 patients with prostate specific antigen and total testosterone values were divided into group A (197 with total testosterone less than 250 ng/dl) and group B (254 with total testosterone 250 ng/dl or greater). The groups differed significantly in free testosterone and sex hormone-binding globulin, but not in age or prostate specific antigen. In group A but not group B prostate specific antigen correlated significantly with total testosterone (r=0.20, p=0.005), free testosterone (r=0.22, p=0.03) and sex hormone-binding globulin (r=0.59, p=0.002) at baseline. After 12 months of testosterone replacement therapy, increase in total testosterone (mean±SD) was statistically significant in group A (+326±295 ng/dl, p<0.001; final total testosterone 516±28 ng/dl) and group B (+154±217 ng/dl, p<0.001; final total testosterone 513±20 ng/dl). After 12 months of testosterone replacement therapy, increase in prostate specific antigen was statistically significant in group A (+0.19±0.61 ng/ml, p=0.02; final prostate specific antigen

1.26±0.96 ng/ml) but not in group B (+0.28±1.18 ng/ml, p=0.06; final prostate specific antigen 1.55±1.72 ng/ml). The average percent prostate specific antigen increase from baseline was higher in group A (21.9%) than in group B (14.1%). Overall the greatest prostate specific antigen was observed after 1 month of treatment and decreased thereafter.

CONCLUSIONS: Patients with baseline total testosterone less than 250 ng/dl were more likely to have an increased prostate specific antigen after testosterone replacement therapy than those with baseline total testosterone 250 ng/dl or greater, supporting the prostate saturation hypothesis. Clinicians should be aware that severely hypogonadal patients may experience increased prostate specific antigen after testosterone replacement therapy.



Purpose: One of the greatest concerns among clinicians regarding testosterone replacement therapy (TRT) is the fear of causing or promoting prostate cancer. We evaluated prostatic changes in hypogonadal men with and without high grade prostatic intraepithelial neoplasia (PIN), which is considered a prostatic precancerous lesion, after 1 year of TRT.

Materials and Methods: A total of 75 hypogonadal who completed 12 months of TRT were studied. All underwent prostate biopsy prior to initiating treatment. Of the men 55 had benign prostate biopsies (PIN) and 20 had PIN without frank cancer (PIN). All men with PIN underwent repeat biopsy to exclude cancer prior to the initiation of testosterone treatment. Prostate specific antigen (PSA), and total and free testosterone were determined prior to treatment and at 1 year. Repeat biopsy was performed for a change noted on digital rectal examination or for a PSA increase of 1 ng/l or greater.

Results: PSA was similar at baseline in men with and without PIN (1.49±1.1 and 1.53±1.6 ng/dl, p 0.05) and after 12 months of TRT (1.82±1.1 and 1.78±1.6 ng/dl, respectively, $p<0.05$). A slight, similar increase in mean PSA was noted in the PIN and PIN groups (0.25±0.6 and 0.33±0.6 ng/dl, $p<0.05$). One man in the PIN group had cancer after biopsy was performed due to abnormal digital rectal examination. Four additional men in the PIN group and 2 in the PIN group underwent re-biopsy

for elevated PSA and none had cancer. No differences were noted between the PIN and PIN groups with regard to total and free testosterone at baseline and at 1 year (p=0.267).

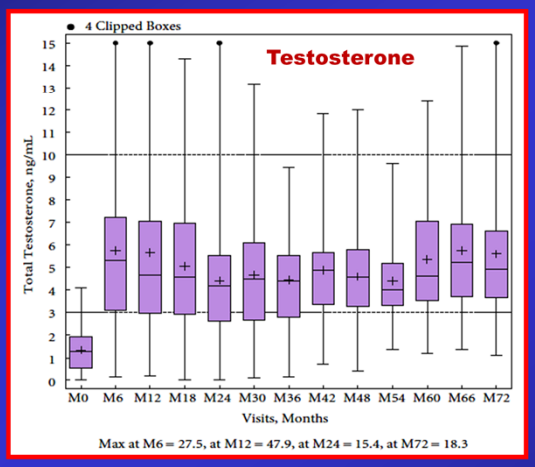
Conclusions: After 1 year of TRT men with PIN do not have a greater increase in PSA or a significantly increased risk of cancer than men without PIN. These results indicate that TRT is not contraindicated in men with a history of PIN.

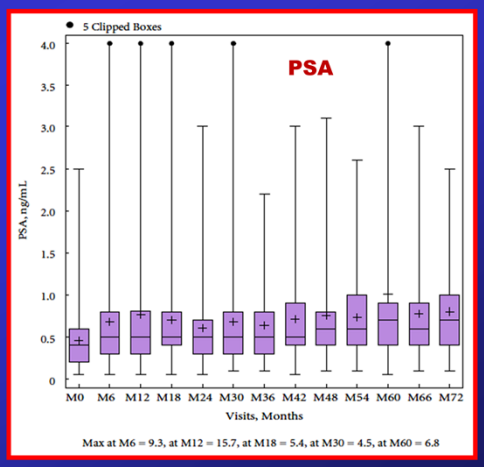
Prostate-specific antigen (PSA) concentrations in hypogonadal men during 6 years of transdermal testosterone treatment

Raynaud JP: BJUI, 2012

200 Men, mean age 41, BMI 26
151 Completed 5 years
Testosterone Patch

PSA Velocity: 0.00–0.03 ng/mL/year
No Cancer; 7 with PSA >4.0 → 6 prostatitis
Baseline Testosterone 1.4 ng/ml (140) PSA 0.47





Objective • To assess the change in prostate-specific antigen (PSA) concentrations in patients with primary or secondary hypogonadism, receiving transdermal testosterone.

Patients and Methods • This was an interventional, 6-year study, conducted in Urology and Endocrinology centres in Belgium, France, Germany, the Netherlands and Spain.

• Participants were primary (48%) or secondary (52%) hypogonadal patients who received two 60 cm^2 testosterone patches (Testopatch®), delivering 4.8 mg of testosterone per day, applied every 2 days.

• During treatment, total testosterone (TT), dihydrotestosterone, oestradiol and, PSA concentrations were measured in a centralised laboratory every 3 months during the first year, and every 6 months thereafter.

Results • In all, 200 patients [mean (sd) age 41.0 (12.5) years, body weight 82.5 (13.7) kg, height 177.2 (9.3) cm, body mass index 26.2 (3.4) kg/m2] were treated with transdermal testosterone patches.

• In all, 161 patients completed the 1-year study and 115 entered into a 5-year study extension; 51 patients completed the sixth year of the study.

• The mean baseline concentrations of TT and PSA were 1.4 ng/mL and 0.47

ng/mL, respectively; TT serum concentrations >3 ng/mL were achieved in 85% of patients and fluctuated between 4.4 and 6.0 ng/mL.

• At each successive 6-month time point, mean the PSA values were 0.60, 0.67, 0.76, 0.70, 0.61, 0.68, 0.64, 0.71, 0.75, 0.74, 1.01, 0.78, 0.80 ng/mL, respectively. The mean PSA velocity was negligible (0.00–0.03 ng/mL/year) from 30 months to the end of the trial, except for a value of 0.08 at 60 months. Seven patients had a PSA concentration of >4 ng/mL due to a sharp PSA increase. Six of these patients had prostatitis and PSA concentrations returned to previous levels with appropriate treatment. No prostate cancer was reported during the trial.

Conclusion • These data support a strong safety profile for Testopatch, even at the highest registered dosage.

Effect of Testosterone Replacement Therapy on Prostate-Specific Antigen (PSA) Levels in Men Being Treated for Hypogonadism: Review and Meta-Analysis

Kang DY, Li HJ: Medicine 94(3): 1-8, 2015

15 Studies (6 gels, 7 IM): 739 treated, 385 controls; 3-12 months; 9 studies had pre & post PSA
PSA increases: Gels **+0.085** (p=0.116) IM **+0.271** (p=0.001)
No difference in number with elevated PSA (>4) or prostate cancer (3 studies)

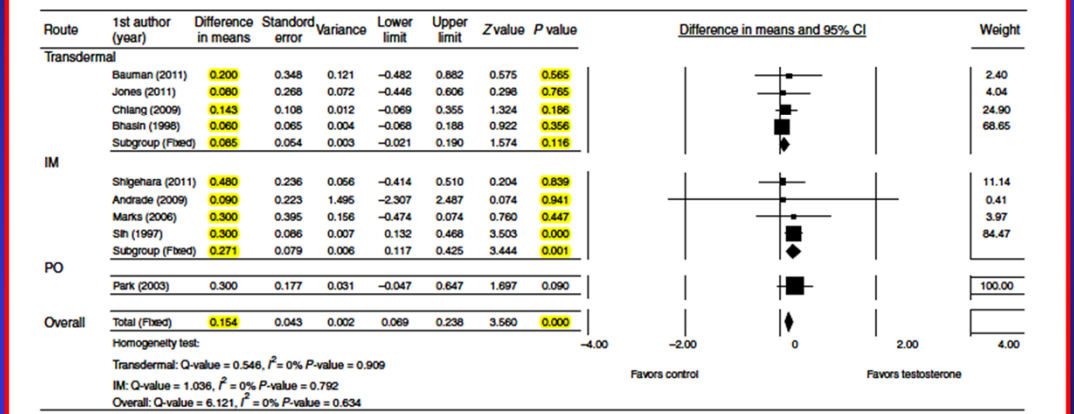


FIGURE 2. Forest plot comparing PSA level change between patients receiving testosterone treatment via transdermal, oral (PO) and intramuscular (IM) routes versus control treatments. CI = confidence interval, Lower limit = lower bound of the 95% CI; Upper limit = upper bound of the 95% CI.

Abstract: Testosterone replacement therapy is used for the treatment of age-related male hypogonadism, and prostate-specific antigen (PSA) is a primary screening tool for prostate cancer. The systematic review and meta-analysis aimed to determine the effect of testosterone replacement therapy on PSA levels.

Medline, Cochrane Library, EMBASE, and Google Scholar databases were searched until February 28, 2014, and inclusion criteria were as follows: randomized controlled trial; intervention group received testosterone/androgen replacement therapy; control group did not receive treatment; and no history of prostate cancer. The primary outcome was change of PSA level between before and after treatment. Secondary outcomes were elevated PSA level after treatment, and the number of patients who developed prostate cancer.

After initially identifying 511 articles, 15 studies with a total of 739 patients that received testosterone replacement and 385 controls were included. The duration of treatment ranged from 3 to 12 months. Patients treated with testosterone tended to have higher PSA levels, and thus a greater change than those that received control treatments (difference in means of PSA levels = 0.154, 95% confidence interval [CI] 0.069 to 0.238, P<0.001). The difference in means of PSA levels were significant higher for patients that received testosterone intramuscularly (IM) than controls (difference in means of PSA levels = 0.271, 95% CI 0.117–0.425, P=0.001).

Elevated PSA levels after treatment were similar between patients that received treatment and controls (odds ratio [OR]=1.02, 95% CI 0.48–2.20, P=0.953). Only 3 studies provided data with respect to the development of prostate cancer, and rates were similar between those that received treatment and controls.

Testosterone replacement therapy does not increase PSA levels in men being treated for hypogonadism, except when it is given IM and even the increase with IM administration is minimal.

(Medicine 94(3):e410)

Finasteride and High-Grade Prostate Cancer in the Prostate Cancer Prevention Trial

Lucia et al (J Natl Cancer Inst 99:1375-83, 2007)

18,882 → Finasteride 5 mg vs Pl
7 years
→ 1,901 Prostate Cancer
Overall: 25% reduction in "cancer"

	Finast	Placebo
Included in analyses†	4368	4692
Diagnosis of prostate cancer	803	1147
Biopsy performed for cause or other procedure‡	1639	1934
Positive for cancer	435	571
End-of-study biopsy§	3652	3820
Positive for cancer	368	576

Table 1. Gleason scores of Prostate Cancer Prevention Trial biopsies through June 23, 2003

	Finasteride			Placebo		
Gleason score	No. of cancers	Percentage of cancers graded	No. having prostatectomy (%)	No. of cancers	Percentage of cancers graded	No. having prostatectomy (%)
2–5	82	10.7	22 (26.8)	160	14.4	50 (31.3)
6	399	51.9	96 (24.1)	699	62.9	161 (23.0)
7	197	25.6	50 (25.4)	193	17.4	56 (29.0)
8–10	91	11.8	38 (41.8)	59	5.3	16 (27.1)
NG*	9	–	3 (33.3)	12	–	3 (25.0)
Total	778	100	209 (26.9)†	1123	100	286 (25.5)†

Background The Prostate Cancer Prevention Trial (PCPT) reported a decreased incidence of prostate cancer overall but an increase in the incidence of high-grade prostate cancer with finasteride compared with placebo. We assessed whether the increased high-grade prostate cancer associated with finasteride in the PCPT was due to finasteride's potential effects on tumor morphology or prostate size.

Methods Prostate biopsies with Gleason score 8 – 10 (n = 90, finasteride; n = 52, placebo) were examined histologically for hormonal effects, and those with Gleason score 7 – 10 (n = 282, finasteride; n = 244, placebo) were examined for pathologic surrogates of disease extent. Prostate volumes were measured at biopsy. Samples from radical prostatectomies (n = 222, finasteride; n = 306, placebo) were examined for tumor grade and extent, and, where possible, grades at biopsy and prostatectomy were compared between the groups. Logistic regression was used to analyze differences between treatment groups with respect to pathologic criteria. All statistical tests were two-sided.

Results Degenerative hormonal changes in high-grade biopsies were equivalent between the finasteride and placebo groups, but prostate volumes were lower in the finasteride group (median = 25.1 versus 34.4 cm^3 ,P <.001). Pathologic surrogates for tumor extent were lower with finasteride than with placebo, including mean percentage of positive cores (34% versus 38%, P = .016), mean tumor linear extent

(greatest [4.4 versus 4.8 mm, *P* = .19] and aggregate [7.6 versus 9.2 mm, *P* = .13]), bilaterally (22.8% versus 30.6%, *P* = .046), and perineural invasion (14.2% versus 20.3%, *P* = .07). Among patients who had prostatectomy, the finasteride-associated increase in high-grade disease (Gleason score ≥ 7) at biopsy (42.7% finasteride versus 25.4% placebo, *P* <.001) was diminished at prostatectomy (46.4% finasteride versus 38.6% placebo, *P* = .10). Biopsy identified a greater proportion of patients with high-grade disease present at prostatectomy in the finasteride group than in the placebo group (69.7% versus 50.5%, *P* = .01). The rate of upgrading (from low-grade cancer at biopsy to high-grade cancer at prostatectomy) and pathologic stage at prostatectomy were similar in both groups.

Conclusions Effects of finasteride on prostate volume and selective inhibition of low-grade cancer, rather than effects on tumor morphology, may have contributed to the increase in high-grade cancers with finasteride in the PCPT. Although induction of high-grade cancer cannot be excluded, the results suggest that high-grade cancer was detected earlier and was less extensive in the finasteride group than in the placebo group.

Prior knowledge Results from the Prostate Cancer Prevention Trial (PCPT) indicated a higher incidence of high-grade prostate cancer among men who were treated with finasteride than men who were treated with placebo.

Study design Disease extent in prostate biopsies with high-grade tumors (Gleason score 7 – 10), prostate gland volume, and tumor grade and extent in radical prostatectomy samples were compared among men who were treated with finasteride and men treated with placebo in the PCPT.

Contributions Men who were treated with finasteride had reduced tumor extent in prostate biopsies and lower prostate gland volumes than men who were treated with placebo. The increase in high-grade disease observed at initial diagnostic needle biopsy in the finasteride group compared with the placebo group was less apparent at prostatectomy. In the finasteride group, needle biopsy identified a larger proportion of the men found to have high-grade disease at prostatectomy. Stage at prostactectomy and the proportion of men with prostate cancer that was upgraded from low grade to high grade at prostatectomy were similar in the two groups.

Implications The increase in high-grade prostate cancer incidence with finasteride observed in the PCPT may have been due in part to effects of finasteride on prostate gland volume and reduced low-grade cancer rather than to effects on tumor morphology or biology.

Limitations Not all men who had biopsies had prostatectomy, and unknown differences among the men who did and did not might have affected the findings in the two groups. This was a multicenter study, and different centers used different methods to prepare prostatectomy samples for analysis, which may have led to variations in the detection of high-grade disease. In addition, long-term outcomes, such as death from prostate cancer or overall survival, were not followed in this study.

Testosterone Replacement for Hypogonadism after Treatment of Early Prostate Cancer with Brachytherapy

Michael F. Sarosdy, MD (Cancer 109:536-41, 2007)

TABLE 1
Disease Characteristics and Treatment of Patients on Testosterone Replacement After Brachytherapy

Characteristic	No. of patients
PSA, ng/mL	
Range	0.4–74
Median	5.3
Gleason score	
5	3
6	19
7	6
8/9	3
Clinical tumor classification	
T1b	1
T1c	20
T2a	8
T2b	2
Cancer treatment	
Brachytherapy	20
Brachytherapy and EBT	11
Brachytherapy with or without EBT combined with androgen blockade	14

PSA indicates prostate-specific antigen; EBT, external beam radiotherapy.

TABLE 2
Testosterone Levels and Duration of Follow-up

Variable	Range	Median
Testosterone, ng/dL		
Pre-TRT	30–255	188
On TRT	356–1373	498
Duration, y		
TRT	0.5–8.5	4.5
Follow-up	1.5–9	5.0

TRT indicates testosterone-replacement therapy.

TABLE 3
Most Recent Prostate-specific Antigen Level in 31 Men on Testosterone-replacement Therapy From 1.5 Years to 9.0 Years After Brachytherapy

PSA, ng/mL	No. of patients (%)
<0.1	23 (74.2)
<0.5	30 (96.7)
<1.0	31 (100)

BACKGROUND. Controversy and a notable paucity of published clinical data best characterize the current knowledge of testosterone-replacement therapy (TRT) for hypogonadism after treatment for early, localized prostate cancer. The objective of this study was to assess the risk of biochemical failure with TRT after treatment of early prostate cancer with permanent transperineal brachytherapy with or without external beam therapy in patients with low serum levels of testosterone and clinical symptoms of hypogonadism.

METHODS. Patients who underwent prostate brachytherapy from 1996 to 2004 and received subsequent TRT for symptomatic hypogonadism were reviewed to detail cancer characteristics and treatment as well as pre- and post-TRT serum testosterone and prostate-specific antigen (PSA) values.

RESULTS. Thirty-one men received TRT after prostate brachytherapy for 0.5 to 8.5 years (median, 4.5 years), with a follow-up that ranged from 1.5 years to 9.0 years (median, 5.0 years) post-brachytherapy. TRT was started from 0.5 years to 4.5 years (median, 2.0 years) after brachytherapy. Serum total testosterone levels ranged from 30 ng/dL to 255 ng/dL (median, 188 ng/dL) before TRT and rose to 365 ng/dL to 1373 ng/dL (median, 498 ng/dL) on TRT. Transient rises in PSA were observed in 1 patient. The most recent PSA level was <0.1 ng/mL in 23 patients (74.2%), <0.5 ng/mL in 30 patients (96.7%), and <1 ng/mL in 31 patients (100%).

No patients stopped TRT because of cancer recurrence or documented cancer progression.

CONCLUSIONS. For patients with low serum testosterone levels and symptoms of hypogonadism, TRT may be used with caution and close follow-up after prostate brachytherapy.

Cancer 2007;109:536–41.

Should testosterone replacement be offered to hypogonadal men treated previously for prostatic carcinoma?

Landau D, Tsakok T, Aylwin S, Hughes S
Clinical Endocrinology 76, 179–181, 2012

Recommend:

- Relapse risk lowest if PSA controlled for 4 years & initially risk low
- Risk/Benefit of untreated hypogonadism vs cancer relapse; involve endo, onco, urology
- Full restaging - re-biopsy should be considered before therapy
- Plan for increased PSA surveillance
- Level of circulating testosterone should be kept as low as possible ??

Table 1. Published series of TRT in men with treated prostate cancer

Authors (year)	Sample size	Prostate cancer treatment	Follow-up (mean/ median, range)	Cases of biochemical recurrence
Kaufman & Graydon (2004)[17]	7	RP	NR, 1–12 years	0
Agarwal & Oefelein (2005)[18]	10	RP	19 months, 9–29 months	0
Khera *et al.* (2009)[19]	57	RP	12 months, 1–60 months	0
Sathyamoorthy *et al.* (2010)[20]	133	RP	363 days, NR	0
Nabulsi *et al.* (2008)[21]	22	RP	24 months, 14–30 months	1
Sarosdy (2007)[22]	31	Brachy	60 months, 18–108 months	0
Morales *et al.* (2009)[23]	5	EBRT	14·6 months, 6–27 months	0
Davila *et al.* (2008)[24]	20	RP (14) EBRT (6)	12 months after RP/9 months after EBRT, NR	0
Leibowitz *et al.* (2010)[25]	96	RP (24) EBRT (12) Brachy (1) ADT (59)	15 months, 1–83 months	41

No Control Group
No Corr with [Testosterone]
PSA reversed when stopped
No Clinical Progression

ADT, androgen deprivation therapy; EBRT, [illegible]
NR, not reported; RP, radical prostatectomy; TRT, testosterone replacement therapy.

Summary Androgen administration can cause prostate cancer progression, and androgen deprivation therapy is a commonly used therapeutic modality in the treatment of prostate cancer. In trying to answer the posed clinical question, this article reviews the risks and benefits of testosterone replacement therapy in this setting and the published data from clinical series. Recommendations are made based on the available evidence.

Clinical background Androgen replacement with testosterone in any of the available formulations is recommended for patients with hypogonadism – both for symptomatic benefit and for its effects on metabolic parameters and body composition. Whilst metastatic or locally persistent prostate cancer is recognized as a contraindication, a dilemma arises in those individuals with a history of previously treated prostate cancer who are in long-term remission. In this article, we consider whether there are individual subjects with previous prostate cancer in whom the risk/benefit ratio favors treatment with androgen replacement.

We have summarized a small number of mostly retrospective case series evaluating the safety of initiating TRT in post-prostatectomy patients with negative margins and undetectable PSA levels. Overall, 42 of 381 (11%, range 0–43%) experienced biochemical recurrence, whilst the majority benefited from symptomatic improvement in their hypogonadism without adverse effects on PSA or tumour

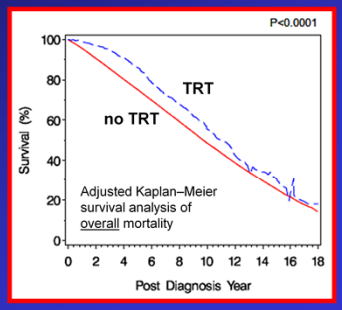
progression. It is likely that research in this field suffers from publication bias as well as the modest quality of most studies. Nevertheless, the data presented here are largely at odds with the longstanding taboo regarding the use of androgens in men with prostate cancer and again raises the question: is it of clinical consequence if a normal serum testosterone level is achieved in a prostate cancer survivor by natural or pharmacological means? Until more studies have been published on this subject, we should take a cautious and conservative approach.

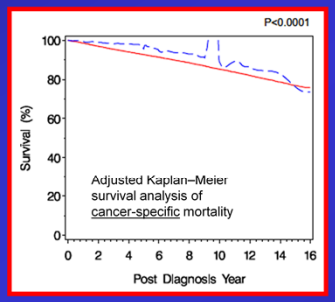
Testosterone Replacement Therapy Following Diagnosis of Prostate Cancer

Kaplan et al: J Sex Med, Jan, 2014

Surveillance, Epidemiology, and End Results - Medicare Data:

149,354 Men Diagnosed with Prostate Cancer 1992-2007 → 1,181 (0.79%) received TRT





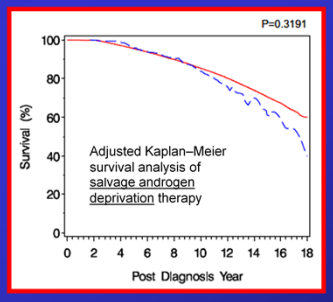


Table 3 Unadjusted mortality and disease severity outcomes for TRT vs. no TRT

Per 100 person years	No TRT	TRT	*P* value
Overall mortality	6.63	4.99	<0.0001
Disease-specific mortality	1.52	0.72	<0.0001
Use of salvage ADT	1.32	1.53	0.0655

ADT = androgen deprivation therapy; TRT = testosterone replacement therapy

Table 4 Adjusted survival and disease severity outcomes in men that used testosterone replacement therapy vs. those that had not

Per 100 person years	No TRT	TRT	*P* value
Overall mortality	6.88	5.40	<0.0001
Disease specific mortality	1.57	0.92	<0.0001
Use of salvage ADT	1.31	1.56	0.1114

The weighted propensity score adjusted for the following: year of diagnosis, age at diagnosis, Charlson comorbidity score, median income, race, education, SEER registry, population density, clinical stage, pathologic grade, PSA screening, preventive testing, and initial treatment modality
ADT = androgen deprivation therapy; TRT = testosterone replacement therapy

Introduction. Late-onset hypogonadism may impair quality of life and contribute to metabolic and cardiovascular comorbidity in aging men. Testosterone replacement therapy is effective in treating hypogonadism. However, for the millions of men with a history of prostate cancer, exogenous testosterone has long been considered contraindicated, even though little data in such men are available. Clarification of this safety issue could allow treatment to be considered for a sizeable segment of the aging male population.

Aim. The aim of this study is to examine population-based utilization and impact of testosterone replacement therapy in men with prostate cancer.

Methods. Using linked Surveillance, Epidemiology, and End Results-Medicare data, we identified 149,354 men diagnosed with prostate cancer from 1992 to 2007. Of those, 1,181 (0.79%) men received exogenous testosterone following their cancer diagnosis. We used propensity scoring analysis to examine the effect of testosterone replacement on the use of salvage hormone therapy and overall and prostate cancer-specific mortality.

Main Outcome Measures. We assessed overall mortality, cancer-specific mortality, and the use of salvage hormone therapy.

Results. Following prostate cancer diagnosis, testosterone replacement was directly related to income and educational status and inversely related to age (all $P < 0.001$). Men undergoing radical prostatectomy and men with well-differentiated tumors were more likely to receive testosterone (all $P < 0.001$). On adjusted analysis, testosterone replacement therapy was not associated with overall or cancer-specific mortality or with the use of salvage hormone therapy.

Conclusions. In this population-based observational study of testosterone replacement therapy in men with a history of prostate cancer, treatment was not associated with increased overall or cancer-specific mortality. These findings suggest testosterone replacement therapy may be considered in men with a history of prostate cancer, but confirmatory prospective studies are needed.

Evolving issues in male hypogonadism: Evaluation, management, and related comorbidities

MARTIN M. MINER
RICHARD SADOVSKY

CLEVE CLIN J MED 74 (SUPPL 3) S38, 2007

Excellent Recent Review:
Differing Levels of Testosterone and the Prostate: a Physiological Interplay

S. Larry Goldenberg, Anthony Koupparis, & Michael E. Robinson
Nature Reviews - Urology 8: 365–377, 2011

TABLE 3
Summary recommendations for prostate monitoring before and during testosterone replacement therapy

Before initiating therapy

Normal digital rectal examination (DRE)

Prostate-specific antigen (PSA) level < 4.0 ng/mL

Evaluate individual risk of prostate cancer[47]

During therapy

Measure PSA:
—At 3 to 6 months
—Semiannually as long as treatment continues

Perform DRE:
—Annually or semiannually as long as treatment continues

Refer for urologic evaluation and possible prostate biopsy in any of the following cases:
—Prostate is abnormal on DRE
—PSA > 4.0 ng/mL
—PSA rises by more than 1 ng/mL after 3 to 4 months on testosterone therapy
—PSA rises at rate > 0.75 ng/mL/yr[42]
—PSA rises at rate > 0.4 ng/mL/yr over an observation period of less than 3 years (using PSA after 6 months on testosterone as reference point)[47]

ABSTRACT Hypogonadism in men has a complex and varied pathogenesis. In addition to multiple established causes of the disease, low testosterone levels are associated with various comorbidities, including metabolic syndrome and type 2 diabetes. Symptoms associated with hypogonadism include reduced sex drive, fatigue, and mood disturbances, but accurate diagnosis requires biochemical testing. Total testosterone is considered the appropriate testosterone measurement in most situations in primary care, although free testosterone is a more accurate marker and is indicated in some situations. Testosterone replacement therapy is a valid treatment option for men with testosterone deficiency accompanied by symptoms of hypogonadism. The goals of therapy are to restore physiologic testosterone levels and alleviate symptoms. A potential association of testosterone replacement therapy with prostate cancer is the biggest safety concern, so patient monitoring should include regular digital rectal examination and prostate-specific antigen tests.

Testosterone: Neuro-Psych

- Dysthymic Disorder (minor depression): Duration ~3.6 yrs
  - 23 Men, ~50 yrs old, Testo 339 ng/dl → 200 mg IM q10-12 days x5
  - Final Testo → 743 ng/dl
  - Remission: 53.8% vs 10%

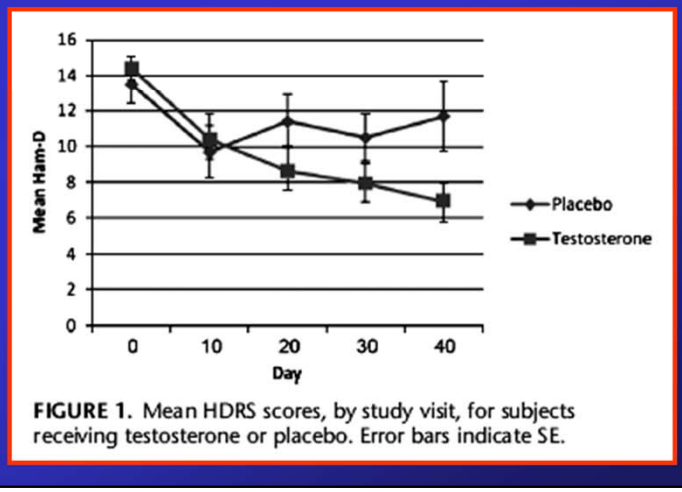


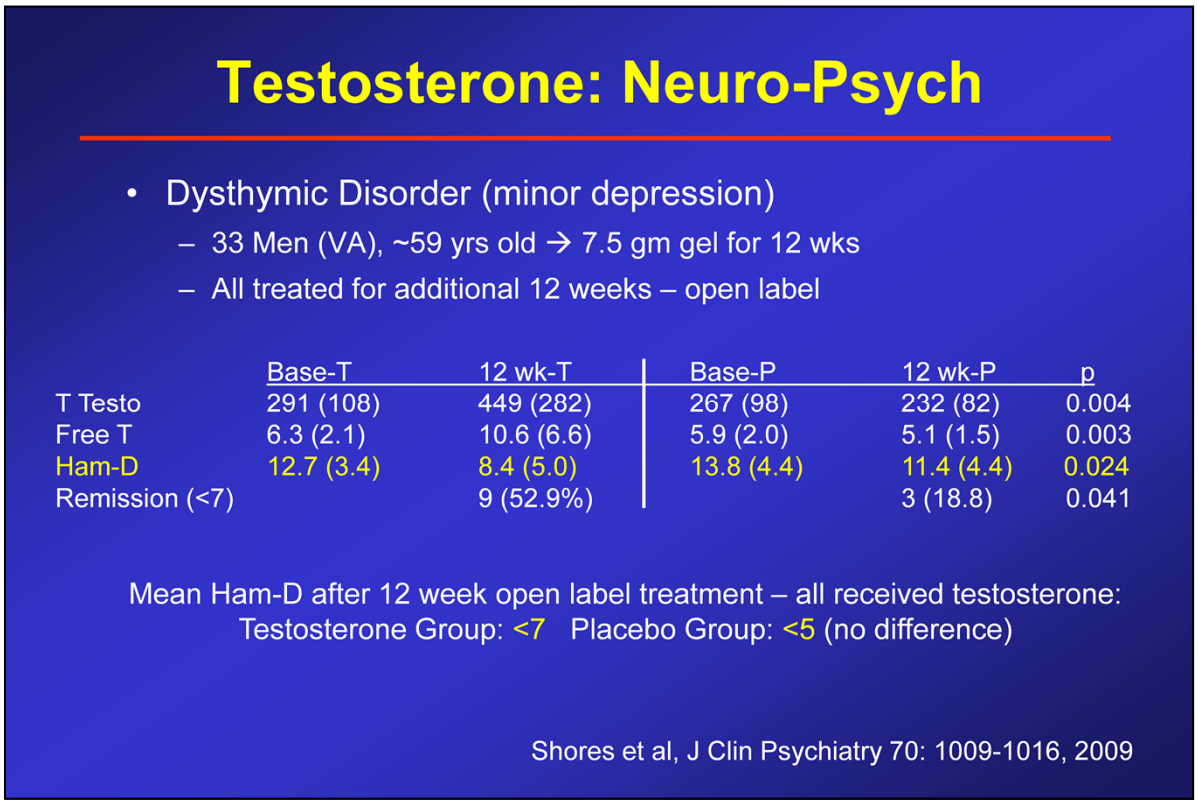
FIGURE 1. Mean HDRS scores, by study visit, for subjects receiving testosterone or placebo. Error bars indicate SE.

Seidman et al
J Clin Psychopharmacol
29: 216-221, 2009

Abstract: Mid<life onset male dysthymic disorder (DD) seems to be a distinct clinical condition with limited therapeutic options. Testosterone replacement is mood<enhancing and has been proposed as an antidepressant therapy, though this strategy has received limited systematic study. We therefore conducted a six-week double-blind placebo-controlled clinical trial in 23 men with DD and with low or low-normal testosterone (T) level (i.e, screening total serum testosterone G350 ng/dL). Enrolled men were randomized to receive intramuscular injections of 200 mg of testosterone cypionate or placebo every 10 days. The primary outcome measures were the Clinical Global Impression (CGI) improvement score and the 21-item Hamilton Depression Rating Scale (HDRS) score.

Twenty-three patients were randomized. The mean (SD) age of the enrolled patients was 50.6 (7.0) years and that of total testosterone level was 339 (93) ng/dL. The median duration of the current dysthymic episode was 3.6 (2.3) years, and the mean (SD) HDRS was 14.0 (2.9). After the intervention, the mean HDRS score decreased significantly more in the testosterone group (7.46 [4.56]) than in the placebo group (1.8 [4.13], t_{21} = -3.07, P = 0.006). Remission, defined as a CGI improvement score of 1 or 2 and a final HDRS score lower than 8, was achieved by 7 (53.8%) of 13 in the testosterone group and 1 (10%) of 10 in the placebo group (P = 0.03).

Testosterone replacement may be an effective antidepressant strategy for late-onset male dysthymia.



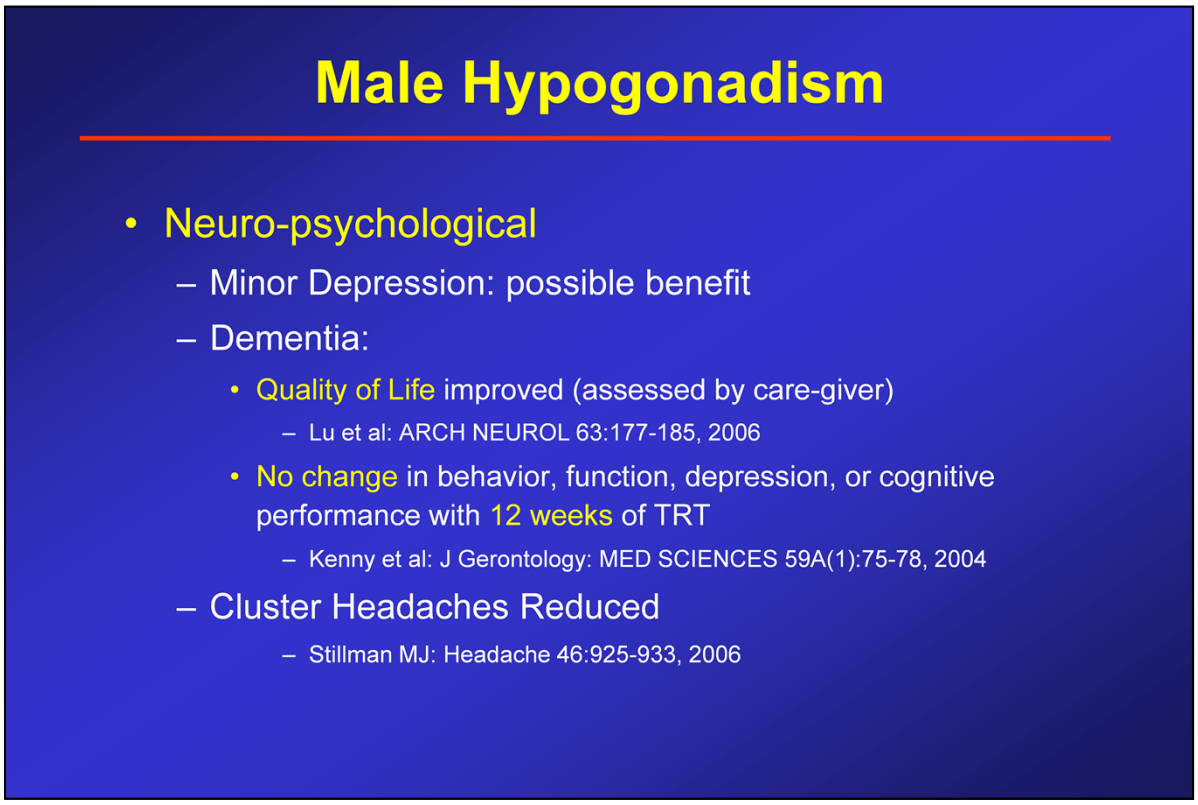
OBJECTIVE: Hypogonadism and subthreshold depression are common conditions in elderly men. The objective of this study was to examine the effect of testosterone treatment in older, hypogonadal men with subthreshold depression.

METHOD: A randomized, double-blind, placebo-controlled study was conducted at a university-affiliated Veterans Affairs Medical Center among men aged 50 years or older (N = 33) with screening total testosterone levels of <or= 280 ng/dL and subthreshold depression (dysthymia or minor depression, according to DSM-IV). Recruitment for the study was conducted from November 2002 through May 2005. Participants received either 7.5 g of testosterone gel or placebo gel daily for 12 weeks, followed by a 12-week open-label extension phase during which all subjects received 7.5 g of testosterone gel. The primary outcome measure was the change in the Hamilton Rating Scale for Depression (HAM-D) score from baseline to the end of the double-blind phase. Secondary outcome measures were remission of subthreshold depression (defined a priori as a HAM-D score <or= 7) and changes in the Hopkins Symptom Checklist depression scale, the Medical Outcomes Study 36-Item Short-Form Health Survey, and the short-form 16-item Quality of Life Enjoyment and Satisfaction Questionnaire.

RESULTS: At the end of the double-blind phase, testosterone-treated men had a greater reduction in HAM-D scores (p = .024) and a higher remission rate of

subthreshold depression (52.9% vs. 18.8%, p = .041) than did placebo-treated men, but there were no differences in other secondary outcome measures between groups. At the end of the open-label phase, the testosterone group had sustained improvement, the control group improved, and there were no differences between groups in any outcome measures.

CONCLUSION: These results suggest that testosterone replacement may be efficacious treatment for subthreshold depression in older men with hypogonadism. Larger studies are needed to corroborate these findings.



Background: There is a compelling need for therapies that prevent, defer the onset, slow the progression, or improve the symptoms of Alzheimer disease (AD).

Objective: To evaluate the effects of testosterone therapy on cognition, neuropsychiatric symptoms, and quality of life in male patients with mild AD and healthy elderly men.

Design: Twenty-four–week, randomized, double-blind, placebo-controlled, parallel-group study.

Setting: Memory disorders clinics as well as general neurology and medicine clinics from University of California medical centers at Los Angeles, San Francisco, and Irvine.

Patients or Other Participants: Sixteen male patients with AD and 22 healthy male control subjects. Healthy elderly control men were recruited from the community through advertisements as well as through the university-based clinics.

Intervention: Testosterone and placebo, in the form of hydroalcoholic gel (75 mg), were applied daily to the skin of the participants.

Main Outcome Measures: Instruments assessing cognitive functioning (Alzheimer's Disease Assessment Scale–Cognitive Subscale, California Verbal Learning Test, Block Design Subtest, Judgment of Line Orientation, Developmental Test of Visual-Motor Integration), neuropsychiatric symptoms (Neuropsychiatric Inventory), global functioning (Clinician's Interview-Based Impression of Change), and quality of life (Quality of Life–Alzheimer Disease Scale).

Results: For the patients with AD, the testosterone-treated group had significantly greater improvements in the scores on the caregiver version of the quality-of-life scale (*P*=.01). No significant treatment group differences were detected in the cognitive scores at end of study, although numerically greater improvement or less decline on measures of visuo-spatial functions was demonstrated with testosterone treatment compared with placebo. In the healthy control group, a non-significant trend toward greater improvement in self-rated quality of life was observed in the testosterone-treated group (*P*=.09) compared with placebo treatment. No difference between the treatment groups was detected in the remaining outcome measures. Testosterone treatment was well tolerated with few adverse effects relative to placebo.

Conclusions: Results suggest that testosterone replacement therapy improved overall quality of life in patients with AD. Testosterone had minimal effects on cognition.

Arch Neurol. 2006;63:177-185

Background. The role of sex hormones in the prevention of cognitive decline is uncertain. Animal studies suggest mechanisms for sex hormones including testosterone to maintain optimal cognitive function. But, there are studies to suggest that endogenous testosterone levels are associated with aggression in men with cognitive impairment.

Methods. In this pilot study, 11 men (mean age 80 6 5 years, range 73–87 years) with early cognitive decline and bioavailable testosterone levels below 128 ng/dl (lower limit for adult normal range) were randomized to receive intramuscular testosterone (200 mg every 3 weeks) or placebo for 12 weeks. Outcome measures included sex hormones (testosterone, bioavailable testosterone, sex hormone binding globulin, estradiol, and estrone), Behave AD Questionnaire, Katz Activities of Daily Living, Geriatric Depression Scale, Digit Span, Clock Face Drawing, Clock Face Perception, Verbal Fluency, Trail-Making B, and International Prostate Symptom Score at baseline, 4 weeks, and 10 weeks.

Results. All men completed the study. Total and bioavailable testosterone, estrone, and estradiol levels increased in men receiving testosterone, but no changes were detected in men receiving placebo. No significant changes were found in behavior following testosterone supplementation, nor was there evidence of change in depression or activities of daily living. No discernable changes were found in any of the cognitive tests. Symptoms of prostate hyperplasia remained unchanged in the testosterone (6.6 $\pm$ 5.8 to 5.2 $\pm$ 3.6; p = 0.39) and placebo (8.8 $\pm$ 6.4 to 6.4 $\pm$ 3.8; p = 0.15) groups, and prostate-specific antigen levels did not change significantly.

Conclusion. No significant changes in behavior, function, depression, or cognitive performance occurred following 12 weeks of testosterone replacement in men with low testosterone levels and early-to-moderate cognitive impairment. This pilot work suggests that testosterone can be given to men with early cognitive impairment without significant concern about worsening aggressive or unwanted behaviors.

Journal of Gerontology: MEDICAL SCIENCES 2004, Vol. 59A, No. 1, 75–78

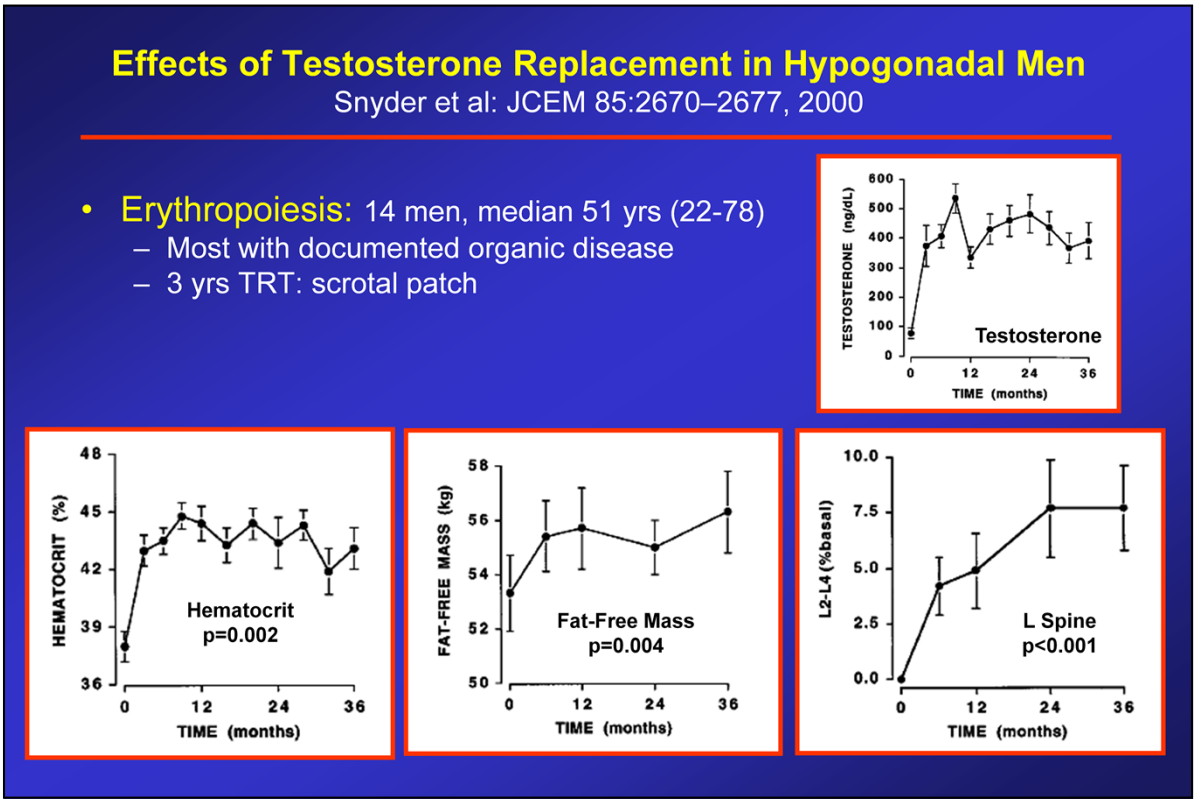
Objectives.—To describe the clinical characteristics and laboratory findings of cluster headache patients whose headaches responded to testosterone replacement therapy.

Background.—Current evidence points to hypothalamic dysfunction, with increased metabolic hyperactivity in the region of the suprachiasmatic nucleus, as being important in the genesis of cluster headaches. This is clinically borne out in the circadian and diurnal behavior of these headaches. For years it has been recognized that male cluster headache patients appear over-masculinized. Recent neuroendocrine and sleep studies now point to an association between gonadotropin and corticotropin levels and hypothalamically entrained pineal secretion of melatonin.

Results.—Seven male and 2 female patients, seen between July 2004 and February 2005, and between the ages of 32 and 56, are reported with histories of treatment resistant cluster headaches accompanied by borderline low or low serum testosterone levels. The patients failed to respond to individually tailored medical regimens, including melatonin doses of 12 mg a day or higher, high flow oxygen, maximally tolerated verapamil, antiepileptic agents, and parenteral serotonin agonists. Seven of the 9 patients met 2004 International Classification for the Diagnosis of Headache criteria for chronic cluster headaches; the other 2 patients had episodic cluster headaches of several months duration. After neurological and physical examination all patients had laboratory investigations including fasting lipid panel, PSA (where indicated), LH, FSH, and testosterone levels (both free and total).

All 9 patients demonstrated either abnormally low or low, normal testosterone levels. After supplementation with either pure testosterone in 5 of 7 male patients or combination testosterone/estrogen therapy in both female patients, the patients achieved cluster headache freedom for the first 24 hours. Four male chronic cluster patients, all with abnormally low testosterone levels, achieved remission.

Conclusions.—Abnormal testosterone levels in patients with episodic or chronic cluster headaches refractory to maximal medical management may predict a therapeutic response to testosterone replacement therapy. In the described cases, diurnal variation of attacks, a seasonal cluster pattern, and previous, transient responsiveness to melatonin therapy pointed to the hypothalamus as the site of neurological dysfunction. Prospective studies pairing hormone levels and polysomnographic data are needed.



ABSTRACT Treatment of hypogonadal men with testosterone has been shown to ameliorate the effects of testosterone deficiency on bone, muscle, erythropoiesis, and the prostate. Most previous studies, however, have employed somewhat pharmacological doses of testosterone esters, which could result in exaggerated effects, and/or have been of relatively short duration or employed previously treated men, which could result in dampened effects. The goal of this study was to determine the magnitude and time course of the effects of physiological testosterone replacement for 3 yr on bone density, muscle mass and strength, erythropoiesis, prostate volume, energy, sexual function, and lipids in previously untreated hypogonadal men.

We selected 18 men who were hypogonadal (mean serum testosterone ± SD, 78 ± 77 ng/dL; 2.7 ± 2.7 nmol/L) due to organic disease and had never previously been treated for hypogonadism. We treated them with testosterone transdermally for 3 yr. Sixteen men completed 12 months of the protocol, and 14 men completed 36 months. The mean serum testosterone concentration reached the normal range by 3 months of treatment and remained there for the duration of treatment. Bone mineral density of the lumbar spine (L2–L4) increased by 7.7 ± 7.6% (P , 0.001), and that of the femoral trochanter increased by 4.0 ± 5.4% (P = 0.02); both reached maximum values by 24 months. Fat-free mass increased 3.1 kg (P = 0.004), and fat-free mass of the arms and legs individually increased, principally within the first 6 months. The decrease in fat mass was not statistically significant. Strength of knee

flexion and extension did not change. Hematocrit increased dramatically, from mildly anemic (38.0 ± 3.0%) to mid-normal (43.1 ± 4.0%; *P* = 0.002) within 3 months, and remained at that level for the duration of treatment. Prostate volume also increased dramatically, from subnormal (12.0 ± 6.0 mL) before treatment to normal (22.4 ± 8.4 mL; *P* = 0.004), principally during the first 6 months. Self-reported sense of energy (49 ± 19% to 66 ± 24%; *P* = 0.01) and sexual function (24 ± 20% to 66 ± 24%; *P* = 0.001) also increased, principally within the first 3 months. Lipids did not change.

We conclude from this study that replacing testosterone in hypogonadal men increases bone mineral density of the spine and hip, fat-free mass, prostate volume, erythropoiesis, energy, and sexual function. The full effect of testosterone on bone mineral density took 24 months, but the full effects on the other tissues took only 3–6 months. These results provide the basis for monitoring the magnitude and the time course of the effects of testosterone replacement in hypogonadal men.

(*J Clin Endocrinol Metab* **85:** 2670–2677, 2000)

Male Hypogonadism

Skin: TRT

increases acne

no other documented effects

Schreiber G & Ziemer M:
JDDG 6:273–280, 2008

Table 3: Hormonal effects on skin aging (after Zouboulis [7]).

Changes in the epidermis
Varying cell count in all layers of the epidermis
Different keratinocyte types
Reduced cell growth in the basement layer
Reduced melanocyte count
Reduced number of Langerhans cells
Flattening of the dermoepidermal zone
Changes in the dermis
Reduced fibroblast number
Diminished collagen synthesis
Thinning and horizontal orientation of collagen fibers
Reduced and abnormal elastic fiber network
Reduced hyaluronic acid synthesis/water-holding capacity
Reduced number of mast cells
Reduced number of vessels
Changes to cutaneous appendages
Diminished hair follicle density
Hair depigmentation
Diminished sweat gland density
Reduced sebum synthesis and increased sebaceous gland volume

Abstract Managing the clinical features of hormone insufficiency in aging men is an important field of activity for dermatologists and in particular for dermatologists specialized in andrology. Potential consequences of age-associated decrease in plasma testosterone levels include long-term changes in diverse organ systems including changes of bone architecture, body composition, muscular strength, cognitive functions, and mood as well as negative effects on skin and hair. Indications and contraindications for a hormone replacement therapy as well as therapy monitoring are well-defined. Replacement of testosterone in the case of late-onset hypogonadism is not a standardized therapy. Previous studies suggest that testosterone replacement therapy has positive clinical effects. Dermatologic effects of testosterone replacement therapy have not yet been investigated. Further research is required to identify potential benefits and risks of hormone replacement therapy in aging men.

Adverse Events Associated With Testosterone Replacement in Middle-Aged and Older Men: A Meta-Analysis of Randomized, Placebo-Controlled Trials

Table 2. Characteristics of Participants

Characteristics	Testosterone Group	Placebo Group
Number of participants	643	427
Age, years	62.9 ± 9.0	64.4 ± 8.2
Baseline testosterone, ng/dl	320 ± 78	344 ± 91
Testosterone levels during treatment, ng/dl	536 ± 173	339 ± 105
Baseline PSA levels, ng/ml	1.3 ± 1.0	1.3 ± 1.0

Note: PSA = prostate-specific antigen.

Only 2/19 studies lasted 3 years
5/19 studies lasted 1 year
12/19 studies <1 year

Calof et al; J Gerontology: Med Sciences 60A(11) 1451–1457, 2005

Table 3. Pooled Odds Ratios for Adverse Events in Primary Analysis

Event	Testosterone Group: Adverse Event Rate per 1000 Patient-Years*	Placebo Group: Adverse Event Rate per 1000 Patient-Years*	Pooled Odds Ratio	95% Confidence Interval
Prostate biopsies	38.7	2.8	1.87	0.84, 4.15
Prostate cancers	9.2	8.3	1.09	0.48, 2.49
PSA >4 ng/ml or 1.5 ng/ml increase during study	57.1	41.6	1.19	0.67, 2.09
Increase in IPSS score	5.5	2.8	1.08	0.46, 2.52
Acute urinary retention	2.2	0	0.99	0.40, 2.44
All prostate events	112.4	55.7	1.78†	1.07, 2.95
Hematocrit >50%	64.5	2.8	3.69†	1.82, 7.51
Atrial fibrillation/arrhythmia	9.2	2.8	1.22	0.53, 2.81
Myocardial infarction	7.4	8.3	0.99	0.44, 2.26
Chest pain/ischemia	7.4	8.3	0.93	0.39, 2.26
Coronary procedure/CABG	3.7	13.9	0.79	0.35, 1.79
Vascular events/cerebrovascular accidents	5.5	11.1	0.86	0.38, 1.95
All cardiovascular events	33.2	44.3	1.14	0.59, 2.20
Death	0	5.5	0.78	0.32, 1.93

Notes: *The rate per 1000 patient-years was calculated based on average study duration of 10 months, standardized to 1 year and multiplied by 1000.
†Odds ratios significantly different from placebo.

BACKGROUND: We performed a meta-analysis of randomized clinical trials to determine the risks of adverse events associated with testosterone replacement in older men.

METHODS: The MEDLINE database was searched from 1966 to April 2004, using testosterone as the indexing term; limits included human, male, > or =45 years old, and randomized controlled trial. Of the 417 studies thus identified, 19 met the inclusion criteria: testosterone replacement for at least 90 days, men > or =45 years old with low or low-normal testosterone level, randomized controlled trial, and medically stable men. Odds ratios (ORs) were pooled using a random effects model, assuming heterogeneous results across studies, and were weighted for sample size.

RESULTS: In the 19 studies that met eligibility criteria, 651 men were treated with testosterone and 433 with placebo. The combined rate of all prostate events was significantly greater in testosterone-treated men than in placebo-treated men (OR = 1.78, 95% confidence interval [CI], 1.07-2.95). Rates of prostate cancer, prostate-specific antigen (PSA) >4 ng/ml, and prostate biopsies were numerically higher in the testosterone group than in the placebo group, although differences between the groups were not individually statistically significant. Testosterone-treated men were nearly four times as likely to have hematocrit >50% as placebo-treated men (OR =

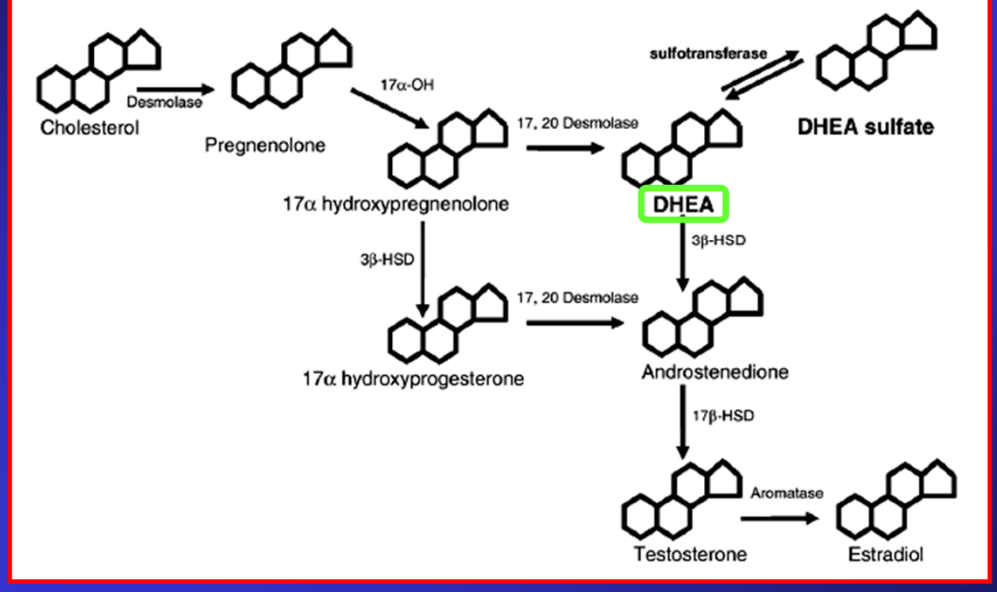
3.69, 95% CI, 1.82-7.51). The frequency of cardiovascular events, sleep apnea or death was not significantly different between the two groups.

CONCLUSIONS: Testosterone replacement in older men was associated with a significantly higher risk of detection of prostate events and of hematocrit >50% than was placebo; hematocrit increase was the most frequent adverse event associated with testosterone replacement. These data reaffirm the need to monitor hematocrit, PSA, and digital examination of the prostate during testosterone replacement in older men.

Male Hypogonadism → TRT

• Sexual Function – Libido, ED	improves (young)
• Bone Metabolism	improves (severe)
• Muscle Mass & Strength	modest increase
• Body Compos, Obesity, Insulin Res	improves
• Lipoproteins	minor decreases
• CVD	suggestive benefit
• Cancer: Prostate, Breast	no harm possible protection
• Neuro-psychological	no harm/minor + depress & h/a?
• Erythropoiesis	improves
• Skin	acne

Male Hypogonadism: DHEA



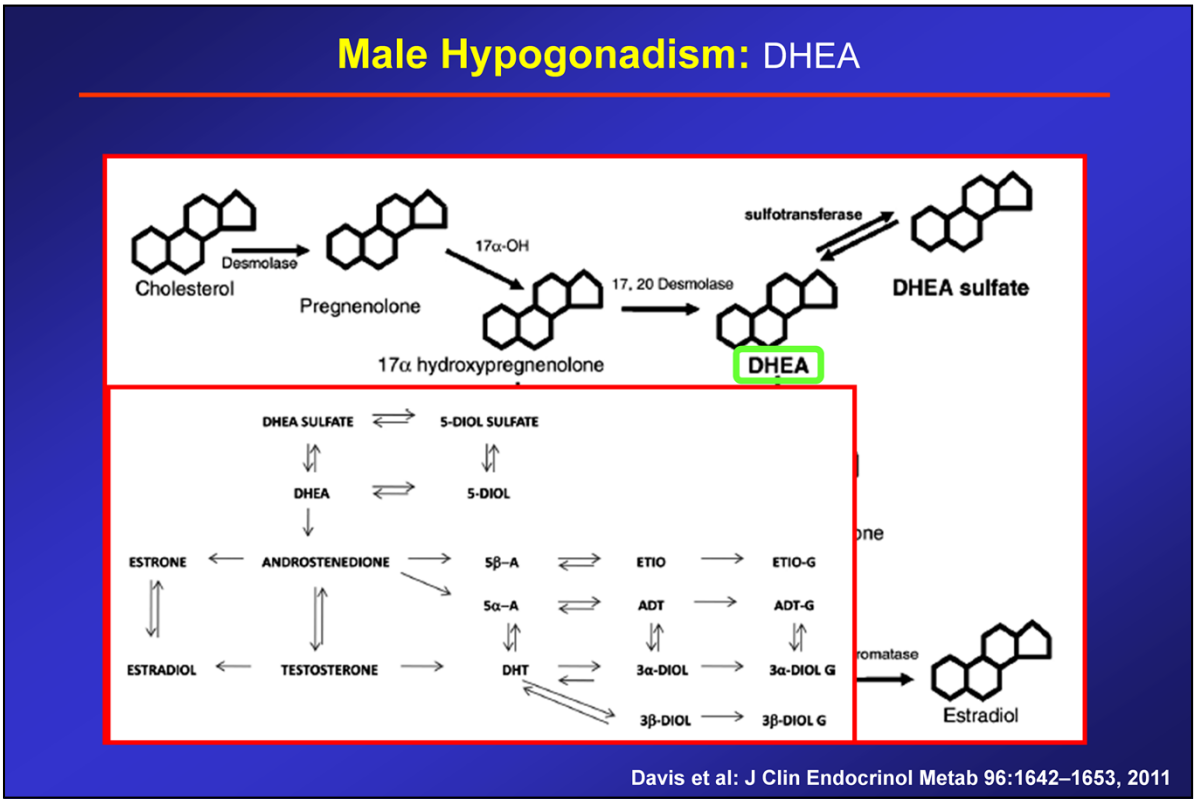
Davis et al: J Clin Endocrinol Metab 96:1642–1653, 2011

CONTEXT: It has been proposed that because dehydroepiandrosterone (DHEA) and its sulfate, DHEAS, are important precursors for estrogen and androgen production, treatment with DHEA is a physiologically based strategy for the alleviation of hormone deficiency symptoms in postmenopausal women. We have summarized the physiology of DHEA in women and reviewed the findings from randomized controlled trials (RCT) of the effects of DHEA therapy in postmenopausal women with normal adrenal function.

EVIDENCE ACQUISITION: We reviewed the medical literature for key papers investigating DHEA physiology and RCT of the use of DHEA in postmenopausal women through November 2010. The focus was on sexual function, well-being, metabolic parameters, and cognition as study endpoints.

EVIDENCE SYNTHESIS: Although cross-sectional studies have indicated a link between low DHEA levels and impaired sexual function, well-being, and cognitive performance in postmenopausal women, placebo-controlled RCT do not show benefits of oral DHEA for any of these outcomes or favorable effects on lipids and carbohydrate metabolism.

CONCLUSIONS: Taken together, findings from this review of the published literature of studies do not support the use of DHEA in postmenopausal women at this time.



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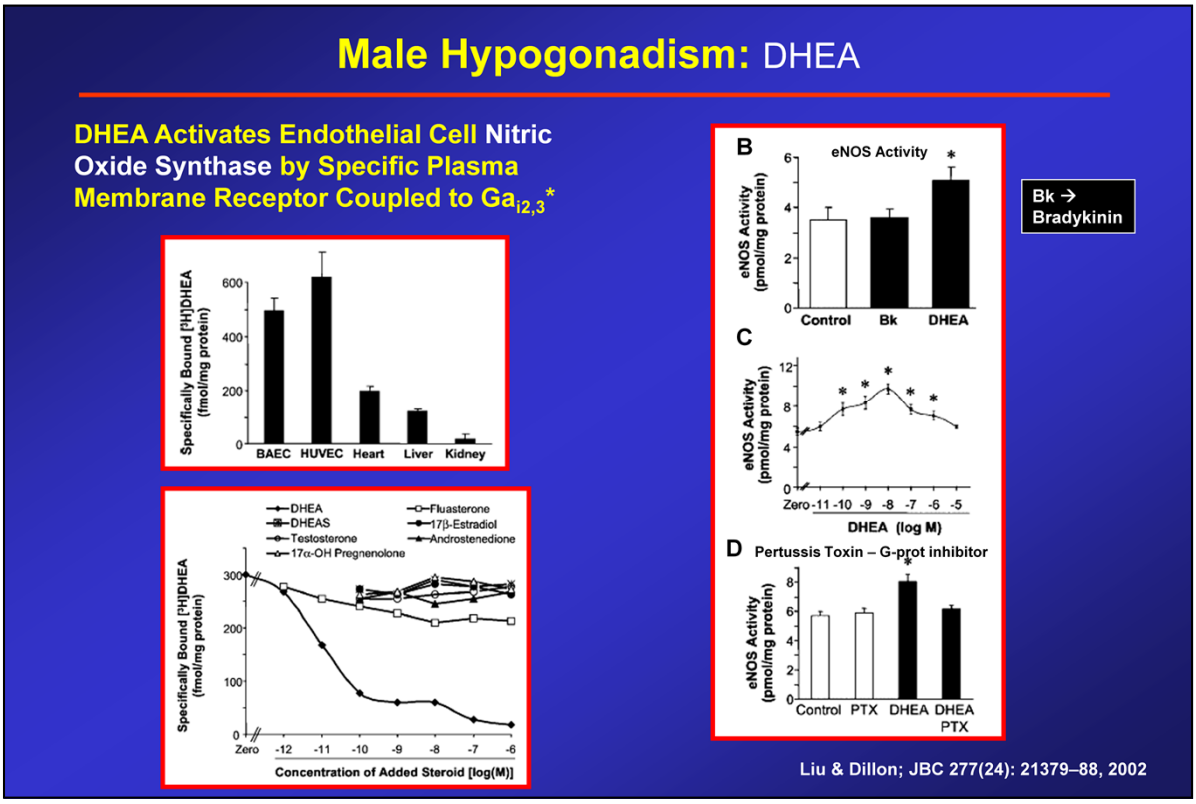


Abstract The adrenal steroid dehydroepiandrosterone (DHEA) has no known cellular receptor or unifying mechanism of action, despite evidence suggesting beneficial vascular effects in humans. Based on previous data from our laboratory, we hypothesized that DHEA binds to specific cell-surface receptors to activate intracellular G-proteins and endothelial nitric-oxide synthase (eNOS). We now pharmacologically characterize a putative plasma membrane DHEA receptor and define its associated G-proteins. The [3H]DHEA binding to isolated plasma membranes from bovine aortic endothelial cells was of **high affinity (K(d) = 48.7 pm)** and **saturable (B(max) = 500 fmol/mg protein).** Structurally related steroids failed to compete with DHEA for binding. The putative DHEA receptor was functionally **coupled to G-proteins**, because guanosine 5'-O-(3-thio)triphosphate (GTPgammaS) inhibited [3H]DHEA binding to plasma membranes by 69%, and DHEA increased [35S]GTPgammaS binding by 157%. DHEA stimulated [35S]GTPgammaS binding to Galpha(i2) and Galpha(i3), but not to Galpha(i1) or Galpha(o). Pretreatment of plasma membranes with antibody to Galpha(i2) or Galpha(i3), but not to Galpha(i1), inhibited the DHEA activation of eNOS. Thus, DHEA receptors are expressed on endothelial cell plasma membranes and are coupled to eNOS activity through Galpha(i2) and Galpha(i3). These novel findings should allow us to isolate the putative receptor and reevaluate the physiological role of DHEA activity.

FIG. 3. Specific binding of [3H]DHEA to plasma membranes of **bovine vascular**

endothelial cells (BAEC), **human umbilical vein endothelial cells (HUVEC),** rat heart, liver, and kidney. Values are expressed as mean S.E. of four separate experiments.

FIG. 4. Competition of **specific [3H]DHEA binding** to plasma membranes of BAEC, by DHEA and structurally related steroids. Membranes (2 g of protein) were incubated at 4 °C for 15 min with 0.1 nM [3H]DHEA, in the absence (*Zero*), or presence of various concentrations of steroids in Tris-HCl buffer, pH 7.4. Nonspecific binding was determined in the presence of excess unlabeled DHEA (10 M), and specific binding represents total minus nonspecific binding. Data are means of three separate experiments, each performed in duplicate.

FIG. 10. Effect of DHEA on eNOS activity in BAEC plasma membranes. The conversion of L-[3H]arginine to L-[3H]citrulline was determined in plasma membranes isolated from BAEC, after a 15-min incubation with buffer alone (*Control*), 1 nM DHEA or 1 M bradykinin (*Bk*) in the absence (*A*), or a **5-min incubation in the presence (*B*), of added calmodulin** and eNOS cofactors. Values are mean S.E. obtained from five to six independent experiments, performed in duplicate. *, *p* 0.05 *versus* control. ***C*, dose-dependent effect of DHEA on eNOS activity.** The conversion of L-[3H]arginine to L-[3H]citrulline was measured in purified plasma membranes incubated in buffer alone (*Zero*), or with various concentrations of DHEA (10 pM to 10 M), with added calmodulin and eNOS cofactors, for 5 min. Values are means S.E., *n* 4. *, *p* 0.05 *versus Zero*. ***D*, effect of PTX on eNOS activation in endothelial cell plasma membranes.** Plasma membranes were isolated from BAEC pretreated with vehicle or 100 ng/ml PTX for 6 h. L-[3H]Arginine conversion to L-[3H]citrulline was measured after 5 min of incubation, in the absence (*Control*) or in the presence of 1 nM DHEA, with eNOS cofactors calcium and calmodulin. Values are means S.E. obtained from four independent experiments, performed in duplicate. *, *p* 0.05 *versus* control.

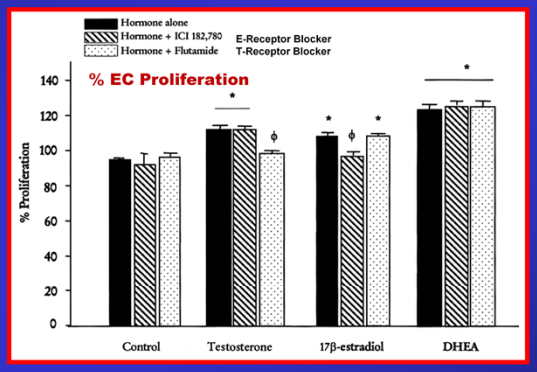
Male Hypogonadism: DHEA

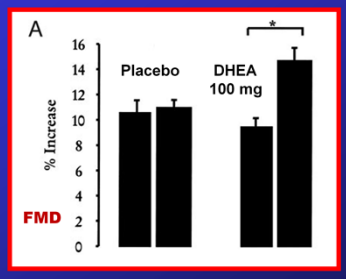
DHEA Increases Endothelial Cell Proliferation *in Vitro* and Improves Endothelial Function *in Vivo* Independent of Androgen & Estrogen Receptors

Increased expression eNOS & ERK1/2 activity

36 Healthy Post-menopausal Women
DHEA 100 mg daily for 3 months (high dose)
S. DHEA ~doubled → Free Testo 2.8 → 13.0
(normal 3.0 to 7.0)

Similar results seen in Human Vascular SM Cells
(Same Group, JCEM 87(1): 176-181, 2002)
ERK1 increased but c-jun & p38 were not
Independent of AR & ER





Williams et al; JCEM 89: 4708–4715, 2004

JCEM 89: 4708–4715, 2004

Abstract Dehydroepiandrosterone (DHEA) may be beneficial in cardiovascular health, but mechanisms of DHEA action in the cardiovascular system are unclear. We have therefore

1) determined DHEA effects on the proliferation of cultured endothelial cells (EC)

2) compared effects of DHEA with estradiol (E) and testosterone (T)

3) examined DHEA effects on subcellular messengers

We have in addition examined effects of DHEA (100 mg/d, 3 months) in 36 healthy postmenopausal women on blood pressure, lipids, and endothelial function, assessed noninvasively in large vessels by **flow-mediated dilation** of the brachial artery during reactive hyperemia, and in small vessels by laser Doppler velocimetry with iontophoresis of acetylcholine. DHEA, E, and T all increased EC proliferation; the effect of E was abolished by the estrogen receptor antagonist ICI 182,780, and that of T was abolished by the androgen receptor antagonist flutamide; neither blocked the effect of DHEA. In vitro, DHEA increased EC expression of endothelial nitric oxide synthase and activity of extracellular signal-regulated kinase 1/2. In vivo, DHEA increased flow-mediated dilation and laser Doppler velocimetry and reduced total plasma cholesterol. Thus, DHEA increases EC proliferation in vitro by mechanism(s) independently of either androgen receptor or estrogen receptor and in vivo enhances large and small vessel EC function in postmenopausal women.

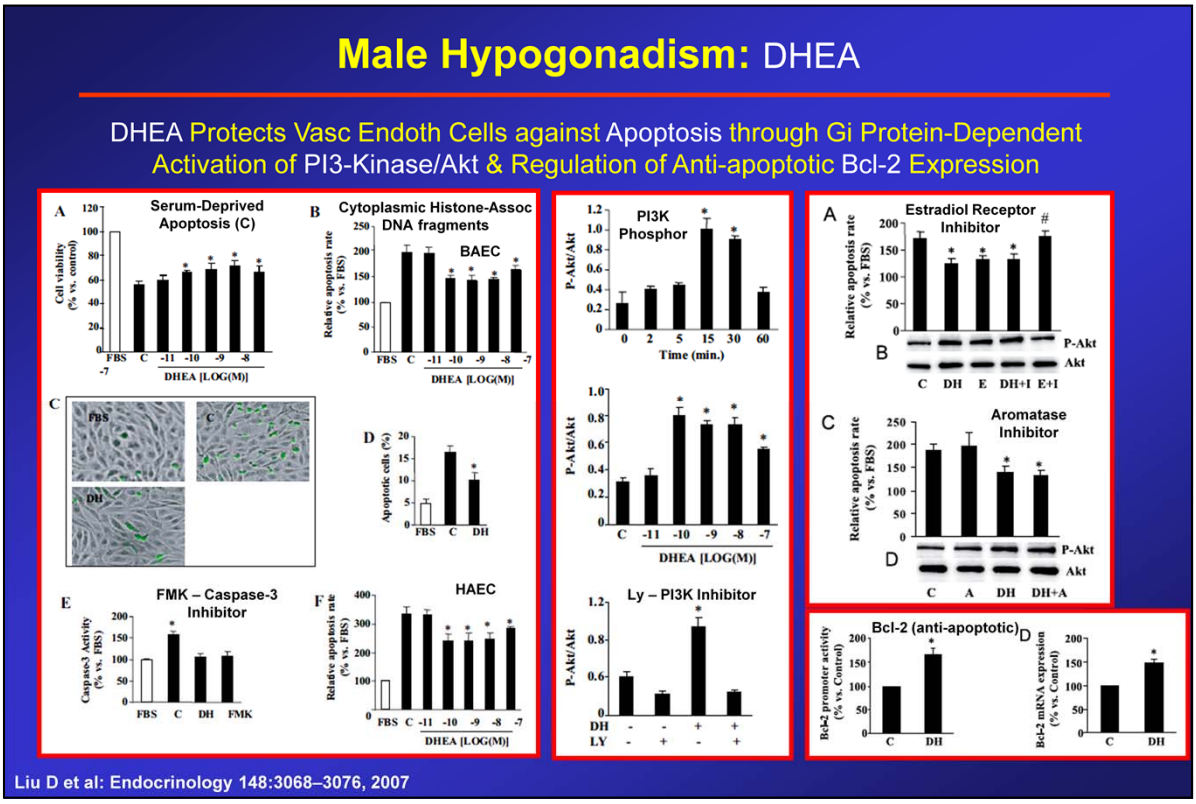
FIG. 2. Effects of the AR antagonist flutamide and the ER antagonist ICI 182,780 on DHEA-induced stimulation of EC proliferation. The AR antagonist flutamide (100 nmol/liter) completely abolishes the stimulatory effects of T (10 nmol/liter), and the ER antagonist ICI 182,780 blocks the effects of 17-E, but neither antagonist affects the stimulatory actions of DHEA on BAEC proliferation. Cells were pretreated with AR or ER antagonists (100 nmol/liter, 2 h) before exposure to steroids (10 nmol/ liter). Data are presented as the mean percentage of FBS stimulation of cell proliferation SEM (n 3). *, Significant difference from FBS-induced increases in cell proliferation; , significant difference from the hormone alone treatment.

FIG. 5. Effects of DHEA on percent FMD in healthy postmenopausal women. A, FMD of the brachial artery with reactive hyperemia is significantly increased after 3 months of DHEA administration (8.4±0.7% to 14.5±1.1%; $P<0.05$; n=18). There were no changes in FMD after placebo treatment (10.8±1.1% to 10.9±0.6%).

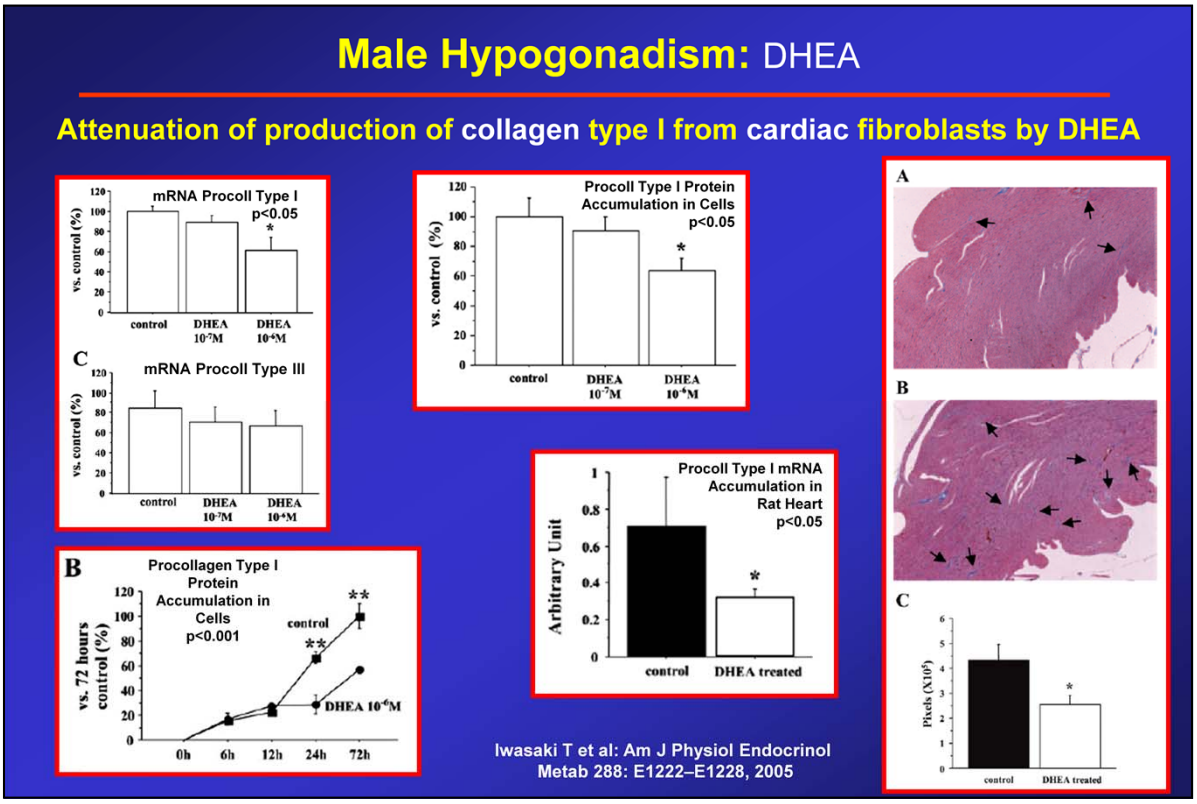
JCEM 87(1): 176-181, 2002

Abstract Dehyroepiandrosterone (DHEA), an adrenal-derived steroid, has been clinically implicated in protection against coronary artery disease and experimentally in inhibition of atherosclerosis and plaque progression. Because DHEA is enzymatically metabolized to androgens or estrogens, it is not clear whether DHEA exerts effects directly or after conversion to these hormones, both of which are associated with well-characterized pathways of action. We therefore examined the effects of DHEA on proliferation of human vascular smooth muscle cells (VSMCs) in culture in the presence or absence of the ER antagonist ICI 182,780 and the AR antagonist flutamide and compared them with the effects of 17beta-estradiol, androstenedione, and T. We also determined the affinity of DHEA for ERs and ARs in VSMC and its specific binding in intact cells. To explore a possible mechanism for DHEA action in these cells, we measured the phosphorylation of ERK-1, c-jun N-terminal protein kinase, and p38 (three members of the MAPK superfamily). Both DHEA and 17beta-estradiol significantly inhibited platelet derived growth factor (PDGF)-BB-induced increases in VSMC proliferation, whereas androstenedione and T increased proliferation. Although E2-induced inhibition of the PDGF effect was abolished by ICI 182,780 and T-induced stimulation was abolished by flutamide, neither receptor antagonist altered the inhibitory effect of DHEA. Binding studies confirmed the presence of both ERs and ARs; DHEA showed minimal affinity for either receptor but bound specifically and with high affinity to putative receptors in intact cells. Following 4-h incubation with DHEA (1-100 nM), ERK1 phosphorylation was significantly reduced in a dose-dependent manner, whereas neither c-jun N-terminal protein kinase nor p38 kinase activity was altered by either PDGF-BB or DHEA. DHEA inhibits human VSMC proliferation by a mechanism independent of

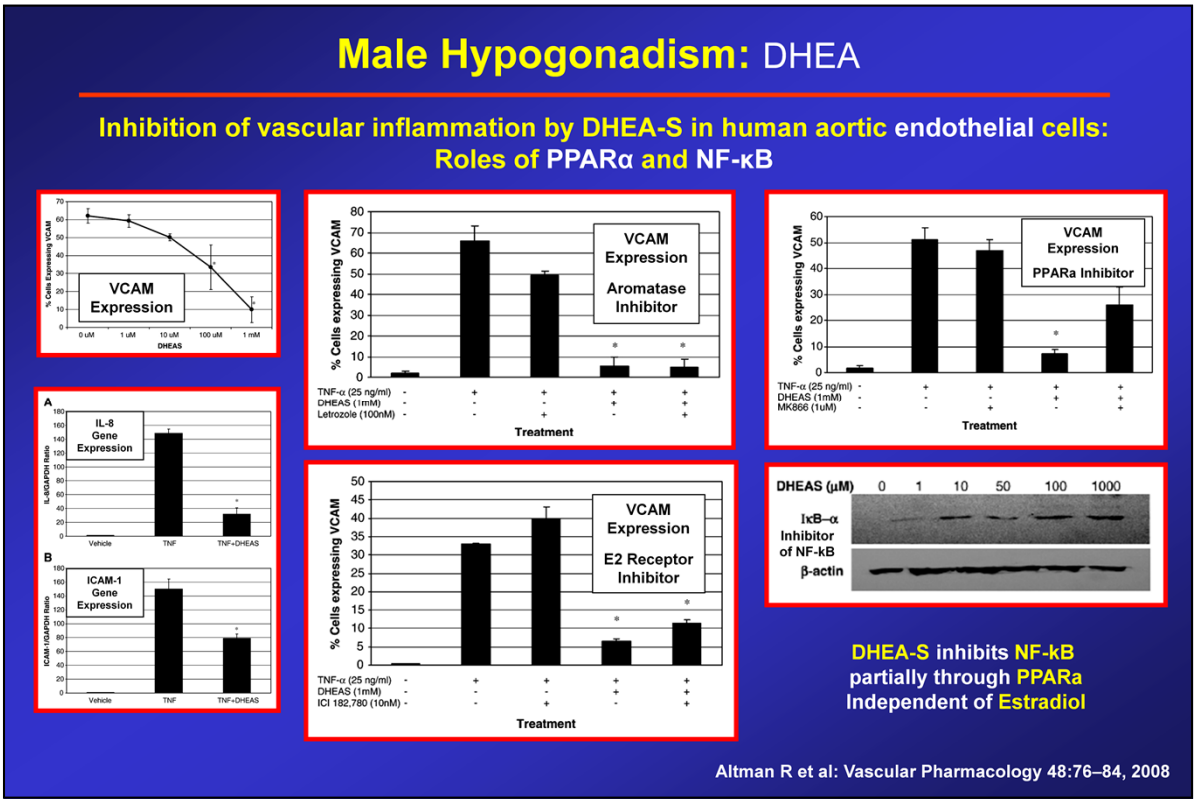
either ARs or ERs, presumably via a DHEA-specific receptor that involves ERK1 signaling pathways.



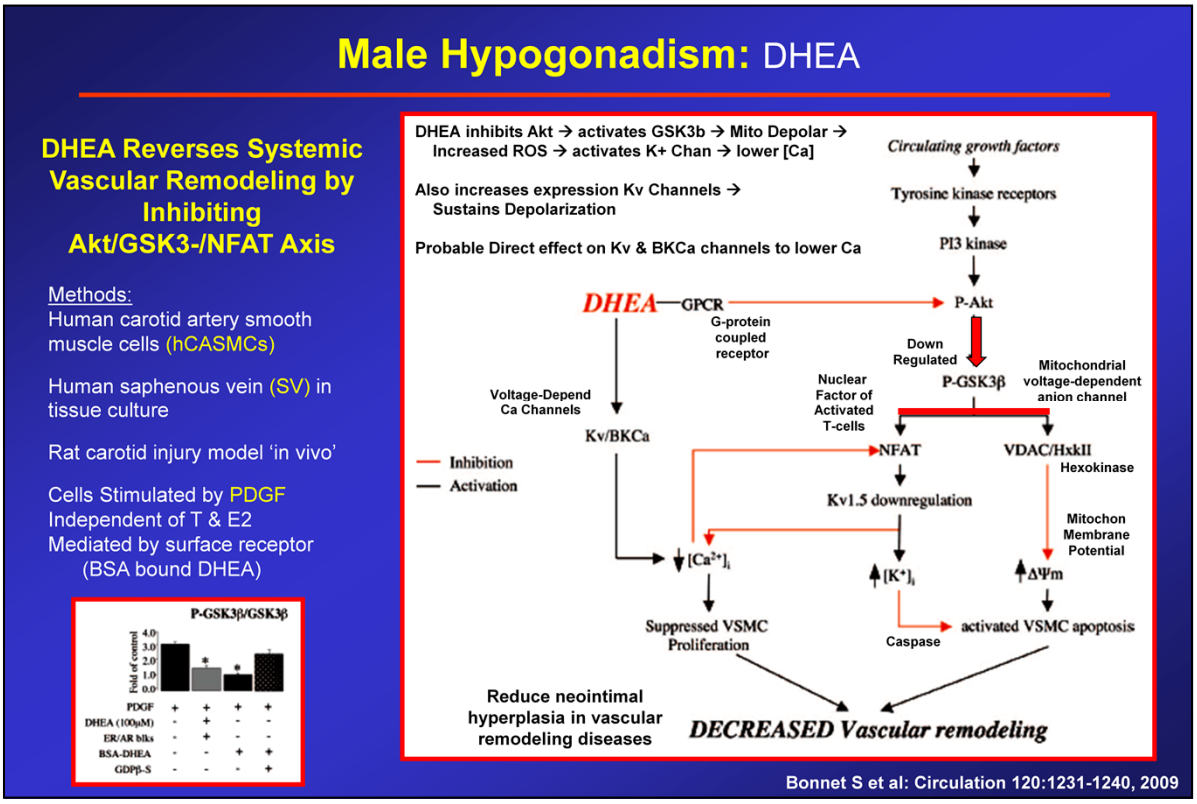
Abstract The adrenal steroid dehydroepiandrosterone (DHEA) may improve vascular function, but the mechanism is unclear. In the present study, we show that DHEA significantly increased cell viability, reduced caspase-3 activity, and protected both bovine and human vascular endothelial cells against serum deprivation-induced apoptosis. This effect was dose dependent and maximal at physiological concentrations (0.1-10 nM). DHEA stimulation of **bovine aortic endothelial cells** resulted in rapid and dose-dependent **phosphorylation of Akt**, which was blocked by LY294002, a specific inhibitor of phosphatidylinositol 3-kinase (PI3K), the upstream kinase of Akt. Accordingly, inhibition of PI3K or transfection of the cells with dominant-negative Akt ablated the anti-apoptotic effect of DHEA. The induced Akt phosphorylation and subsequent **cytoprotective effect of DHEA** were dependent on activation of Galphai proteins, but were estrogen receptor independent, because these effects were blocked by pertussis toxin but not by the estrogen receptor inhibitor ICI182,780 or the aromatase inhibitor aminoglutethimide. Finally, DHEA enhanced anti-apoptotic Bcl-2 protein expression, its promoter activity, and gene transcription attributable to the activation of the PI3K/Akt pathway. Neutralization of Bcl-2 by antibody transfection significantly decreased the anti-apoptotic effect of DHEA. These findings provide the first evidence that **DHEA acts as a survival factor for endothelial cells** by triggering the Galphai-PI3K/Akt-Bcl-2 pathway to protect cells against apoptosis. This may represent an important mechanism underlying the vascular protective effect of DHEA.



Abstract Dehydroepiandrosterone (DHEA) is a type of adrenal steroid. The concentrations of DHEA and its sulfate (DHEA-S) in serum reach a peak between the ages of 25 and 30 yr and thereafter decline steadily. It was reported that DHEA-S concentration in humans is inversely related to death from cardiovascular diseases. In this study, we examined the effects of DHEA on regulation of collagen mRNA and collagen synthesis in cultured cardiac fibroblasts. Treatment with DHEA (10(-6) M) resulted in a significant decrease in procollagen type I mRNA expression compared with controls. This was accompanied by a significant decrease in procollagen type I protein accumulation in the medium and also a significant decrease in procollagen type I protein synthesis in the cellular matrix. Furthermore, to confirm in vitro results, we administered DHEA to Sprague-Dawley rats, which were treated with angiotensin II for 8 wk to induce cardiac damage. Procollagen type I mRNA expression was significantly decreased and cardiac fibrosis significantly inhibited in DHEA-treated rat hearts without lowering the systolic blood pressure. These results strongly indicate that DHEA can directly attenuate collagen type I synthesis at the transcriptional level in vivo and in vitro in cardiac fibroblasts.



Abstract Dehydroepiandrosterone sulfate (DHEAS) is a hormone produced by the adrenal gland and is a precursor for both androgens and estrogens. Atherosclerosis is a well characterized inflammatory disease, but little is known about the role of DHEAS in vascular inflammation. We hypothesize that DHEAS can reduce inflammation in vascular endothelial cells and the mechanism involves the peroxisome proliferator-activated receptor alpha (PPAR alpha), thereby inhibiting transcription factors involved in endothelial cell inflammation. To test our hypothesis, aortic endothelial cells were pretreated for 48 h with DHEAS, then with TNF-alpha. TNF-alpha-induced upregulation of the expression of inflammatory genes interleukin (IL)-8 and intracellular adhesion molecule (ICAM)-1 was attenuated by incubation with DHEAS. DHEAS inhibited the TNF-alpha-induced surface expression of vascular cell adhesion molecule (VCAM)-1. This effect was abolished by the addition of MK866, a PPAR alpha inhibitor, indicating that PPAR alpha is involved in the mechanism of this inhibition. The addition of the aromatase inhibitor letrozole had no effect on the inhibition of TNF-alpha-induced VCAM-1 expression by DHEAS. Treatment of endothelial cells with DHEAS dramatically inhibited the TNF-alpha-induced activation of NF-kappaB, an inflammatory transcription factor, and increased protein levels of the NF-kappaB inhibitor, I-kappaB-alpha. These results signify the ability of DHEA-S to directly inhibit the inflammatory process and show a potential direct effect of DHEAS on vascular inflammation that has implications for the development of atherosclerotic cardiovascular disease.

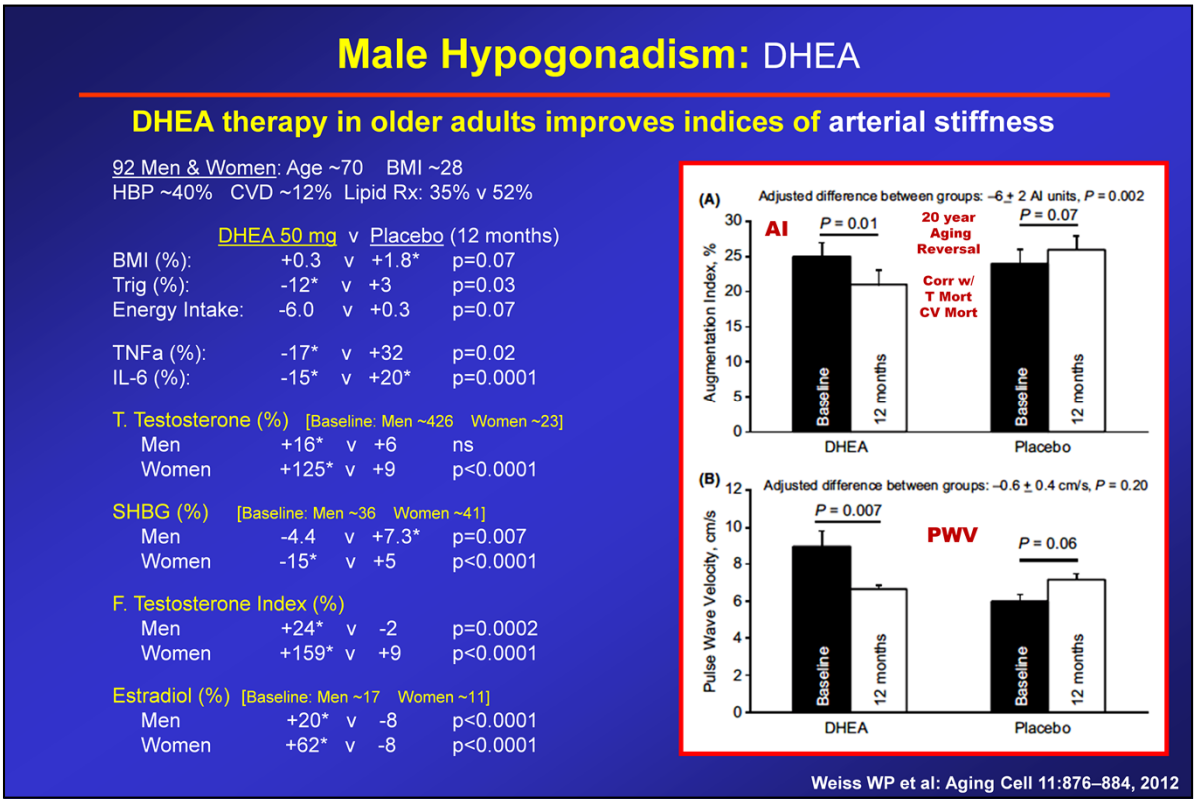


BACKGROUND: The remodeled vessel wall in many vascular diseases such as restenosis after injury is characterized by proliferative and apoptosis-resistant vascular smooth muscle cells. There is evidence that proproliferative and antiapoptotic states are characterized by a metabolic (glycolytic phenotype and hyperpolarized mitochondria) and electric (downregulation and inhibition of plasmalemmal K(+) channels) remodeling that involves activation of the Akt pathway. Dehydroepiandrosterone (DHEA) is a naturally occurring and clinically used steroid known to inhibit the Akt axis in cancer. We hypothesized that DHEA will prevent and reverse the remodeling that follows vascular injury.

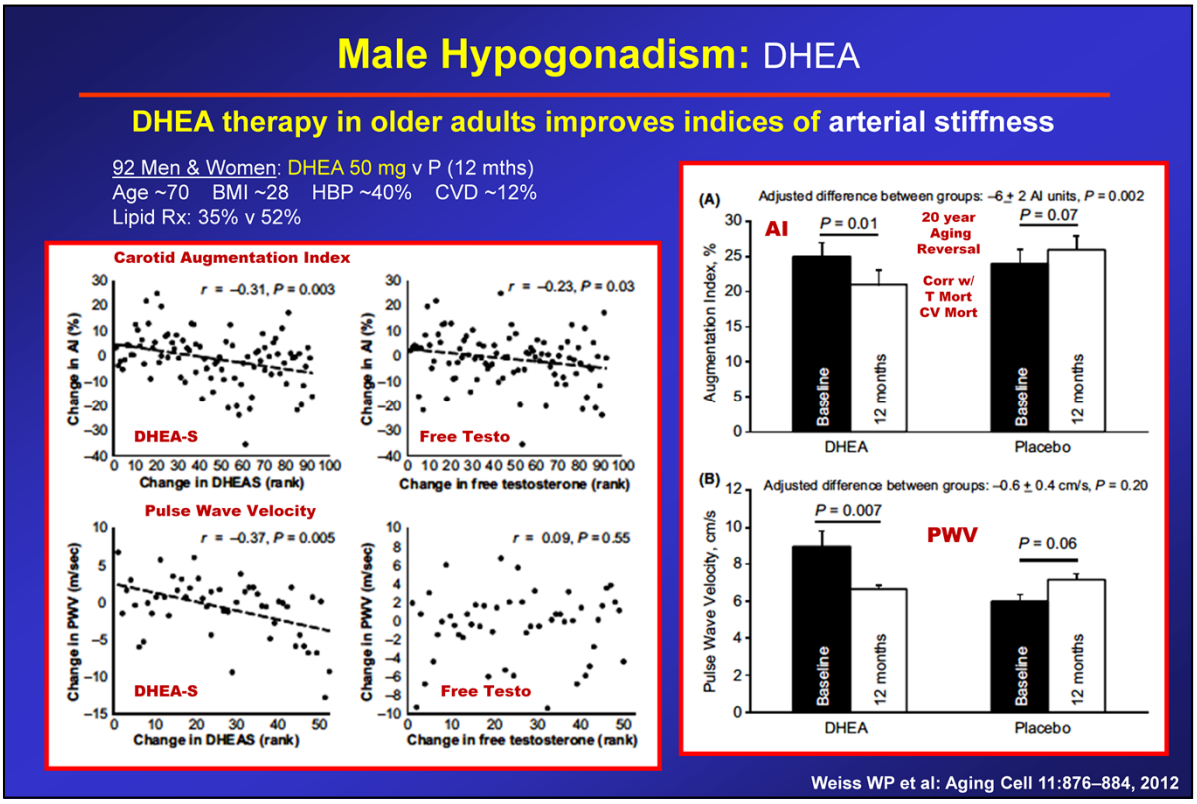
METHODS AND RESULTS: We used cultured human carotid vascular smooth muscle cell and saphenous vein grafts in tissue culture, stimulated by platelet-derived growth factor to induce proliferation in vitro and the rat carotid injury model in vivo. DHEA decreased proliferation and increased vascular smooth muscle cell apoptosis in vitro and in vivo, reducing vascular remodeling while sparing healthy tissues after oral intake. Using pharmacological (agonists and antagonists of Akt and its downstream target glycogen-synthase-kinase-3beta [GSK-3beta]) and molecular (forced expression of constitutively active Akt1) approaches, we showed that the effects of DHEA were mediated by inhibition of Akt and subsequent activation of GSK-3beta, leading to mitochondrial depolarization, increased reactive oxygen species, activation of redox-sensitive plasmalemmal voltage-gated K(+) channels, and decreased [Ca(2+)](i). These functional changes were accompanied

by sustained molecular effects toward the same direction; by decreasing [Ca(2+)](i) and inhibiting GSK-3beta, DHEA inhibited the nuclear factor of activated T cells transcription factor, thus increasing expression of Kv channels (Kv1.5) and contributing to sustained mitochondrial depolarization. These results were independent of any steroid-related effects because they were not altered by androgen and estrogen inhibitors but involved a membrane G protein-coupled receptor.

CONCLUSIONS: We suggest that the orally available DHEA might be an attractive candidate for the treatment of systemic vascular remodeling, including restenosis, and we propose a novel mechanism of action for this important hormone and drug.



Abstract Serum dehydroepiandrosterone (DHEA) concentrations decrease approximately 80% between ages 25 and 75 year. Aging also results in an increase in arterial stiffness, which is an independent predictor of cardiovascular disease (CVD) risk and mortality. Therefore, it is conceivable that DHEA replacement in older adults could reduce arterial stiffness. We sought to determine whether DHEA replacement therapy in older adults reduces **carotid augmentation index (AI)** and **carotid-femoral pulse wave velocity (PWV)** as indices of arterial stiffness. A randomized, double-blind trial was conducted to study the effects of 50 mg day(-1) DHEA replacement on AI (n = 92) and PWV (n = 51) in women and men aged 65-75 year. Inflammatory cytokines and sex hormones were measured in fasting serum. AI decreased in the DHEA group, but not in the placebo group (difference between groups, -6 ± 2 AI units, P = 0.002). Pulse wave velocity also decreased (difference between groups, -3.5 ± 1.0 m s(-1), P = 0.001); however, after adjusting for baseline values, the between-group comparison became nonsignificant (P = 0.20). The reductions in AI and PWV were accompanied by decreases in inflammatory cytokines (tumor necrosis factor α and IL-6, P < 0.05) and correlated with increases in serum DHEAS (r = -0.31 and -0.37, respectively, P < 0.05). The reductions in AI also correlated with free testosterone index (r = -0.23, P = 0.03). In conclusion, DHEA replacement in elderly men and women improves indices of arterial stiffness. Arterial stiffness increases with age and is an independent risk factor for CVD. Therefore, the improvements observed in this study suggest that DHEA replacement might partly reverse arterial aging and reduce CVD risk.



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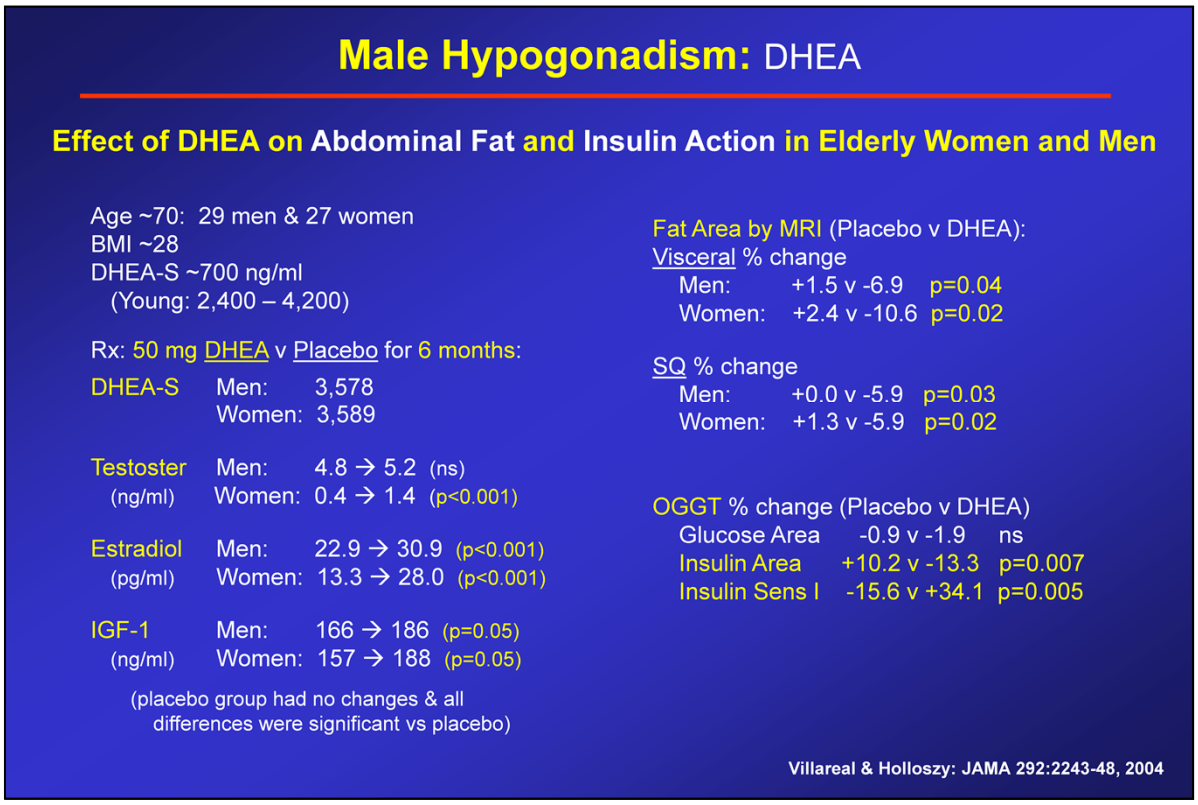


CONTEXT: Dehydroepiandrosterone (DHEA) administration has been shown to reduce accumulation of abdominal visceral fat and protect against insulin resistance in laboratory animals, but it is not known whether DHEA decreases abdominal obesity in humans. DHEA is widely available as a dietary supplement without a prescription.

OBJECTIVE: To determine whether DHEA replacement therapy decreases abdominal fat and improves insulin action in elderly persons.

DESIGN AND SETTING: Randomized, double-blind, placebo-controlled trial conducted in a US university-based research center from June 2001 to February 2004.

PARTICIPANTS: Fifty-six elderly persons (28 women and 28 men aged 71 [range, 65-78] years) with age-related decrease in DHEA level.

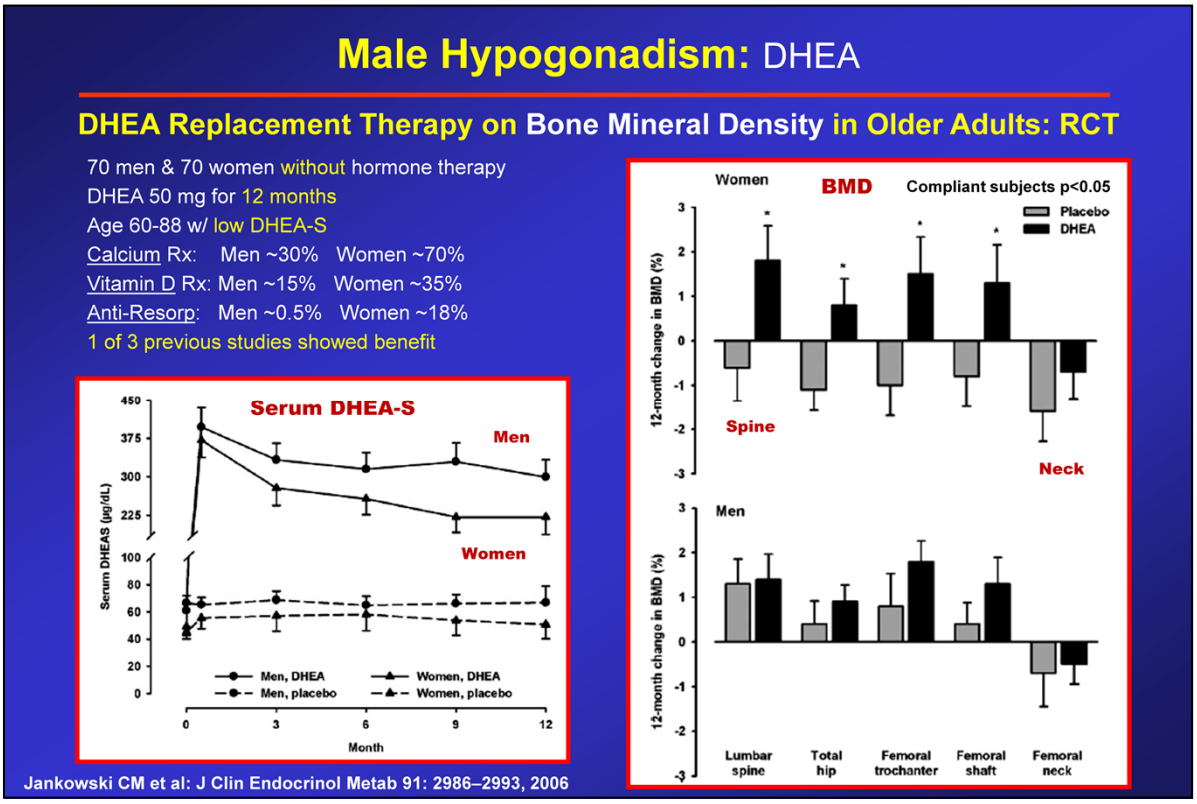
INTERVENTION: Participants were randomly assigned to receive 50 mg/d of DHEA or matching placebo for 6 months.

MAIN OUTCOME MEASURES: The primary outcome measures were 6-month

change in visceral and subcutaneous abdominal fat measured by magnetic resonance imaging and glucose and insulin responses to an oral glucose tolerance test (OGTT).

RESULTS: Of the 56 men and women enrolled, 52 underwent follow-up evaluations. Compliance with the intervention was 97% in the DHEA group and 95% in the placebo group. Based on intention-to-treat analyses, DHEA therapy compared with placebo induced significant decreases in visceral fat area (-13 cm2 vs +3 cm2, respectively; P = .001) and subcutaneous fat (-13 cm2 vs +2 cm2, P = .003). The insulin area under the curve (AUC) during the OGTT was significantly reduced after 6 months of DHEA therapy compared with placebo (-1119 muU/mL per 2 hours vs +818 muU/mL per 2 hours, P = .007). Despite the lower insulin levels, the glucose AUC was unchanged, resulting in a significant increase in an insulin sensitivity index in response to DHEA compared with placebo (+1.4 vs -0.7, P = .005).

CONCLUSION: DHEA replacement could play a role in prevention and treatment of the metabolic syndrome associated with abdominal obesity.



CONTEXT: Dehydroepiandrosterone (DHEA) and its sulfate (DHEAS) decrease with aging and are important androgen and estrogen precursors in older adults. Declines in DHEAS with aging may contribute to physiological changes that are sex hormone dependent.

OBJECTIVE: The aim was to determine whether DHEA replacement increases bone mineral density (BMD) and fat-free mass.

DESIGN, SETTING, AND PARTICIPANTS: A randomized, double-blinded, controlled trial was conducted at an academic research institution. Participants were 70 women and 70 men, aged 60-88 yr, with low serum DHEAS levels.

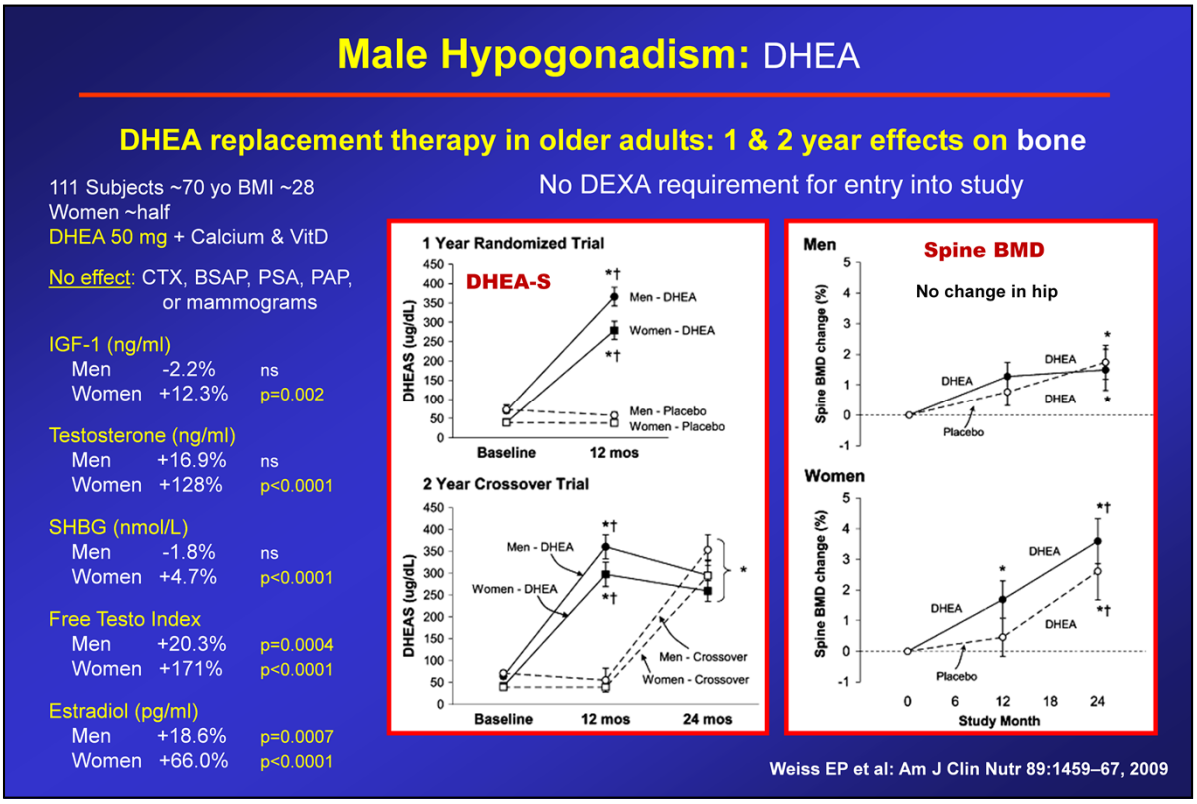
INTERVENTION: The intervention was oral DHEA 50 mg/d or placebo for 12 months.

MEASUREMENTS: BMD, fat mass, and fat-free mass were measured before and after intervention.

RESULTS: Intent-to-treat analyses revealed trends for DHEA to increase BMD more than placebo at the total hip (1.0%, P = 0.05), trochanter (1.2%, P = 0.06), and

shaft (1.2%, P = 0.05). In women only, DHEA increased lumbar spine BMD (2.2%, P = 0.04; sex-by-treatment interaction, P = 0.05). In secondary compliance analyses, BMD increases in hip regions were significant (1.2-1.6%; all P < 0.02) in the DHEA group. There were no significant effects of DHEA on fat or fat-free mass in intent-to-treat or compliance analyses.

CONCLUSIONS: DHEA replacement therapy for 1 yr improved hip BMD in older adults and spine BMD in older women. Because there have been few randomized, controlled trials of the effects of DHEA therapy, these findings support the need for further investigations of the benefits and risks of DHEA replacement and the mechanisms for its actions.



BACKGROUND: Age-related reductions in serum dehydroepiandrosterone (DHEA) concentrations may be involved in bone mineral density (BMD) losses.

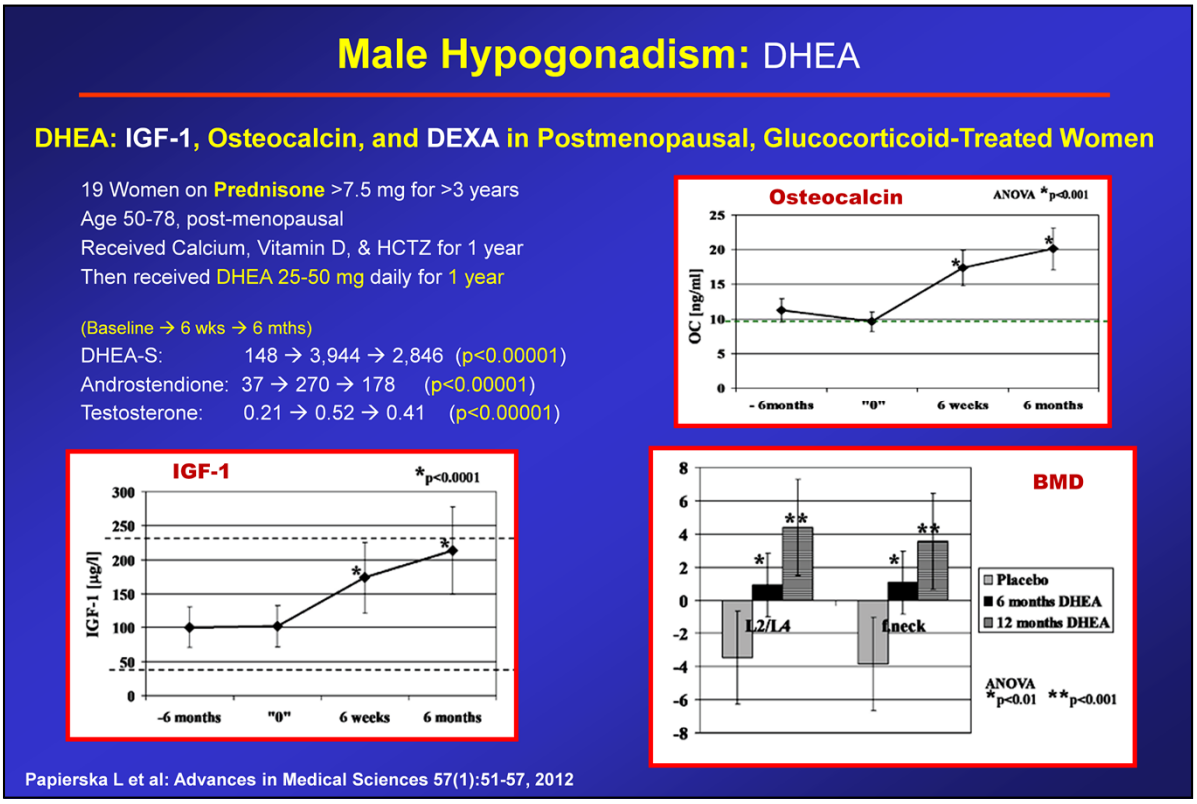
OBJECTIVE: The objective was to determine whether DHEA supplementation in older adults improves BMD when co-administered with vitamin D and calcium.

DESIGN: In year 1, a randomized trial was conducted in which men (n = 55) and women (n = 58) aged 65-75 y took 50 mg/d oral DHEA supplements or placebo. In year 2, all participants took open-label DHEA (50 mg/d). During both years, all participants received vitamin D (16 microg/d) and calcium (700 mg/d) supplements. BMD was measured by using dual-energy X-ray absorptiometry. Concentrations of hormones and bone turnover markers were measured in serum.

RESULTS: In men, no difference between groups occurred in any BMD measures or in bone turnover markers during year 1 or year 2. The free testosterone index and estradiol increased in the DHEA group only. In women, spine BMD increased by 1.7 +/- 0.6% (P = 0.0003) during year 1 and by 3.6 +/- 0.7% after 2 y of supplementation in the DHEA group; however, in the placebo group, spine BMD was unchanged during year 1 but increased to 2.6 +/- 0.9% above baseline during year 2 after the crossover to DHEA. Hip BMD did not change. Testosterone, estradiol, and insulin-like growth factor 1 increased in the DHEA group only. In both

groups, serum concentrations of bone turnover markers decreased during year 1 and remained low during year 2, but did not differ between groups.

CONCLUSION: DHEA supplementation in older women, but not in men, improves spine BMD when co-administered with vitamin D and calcium.



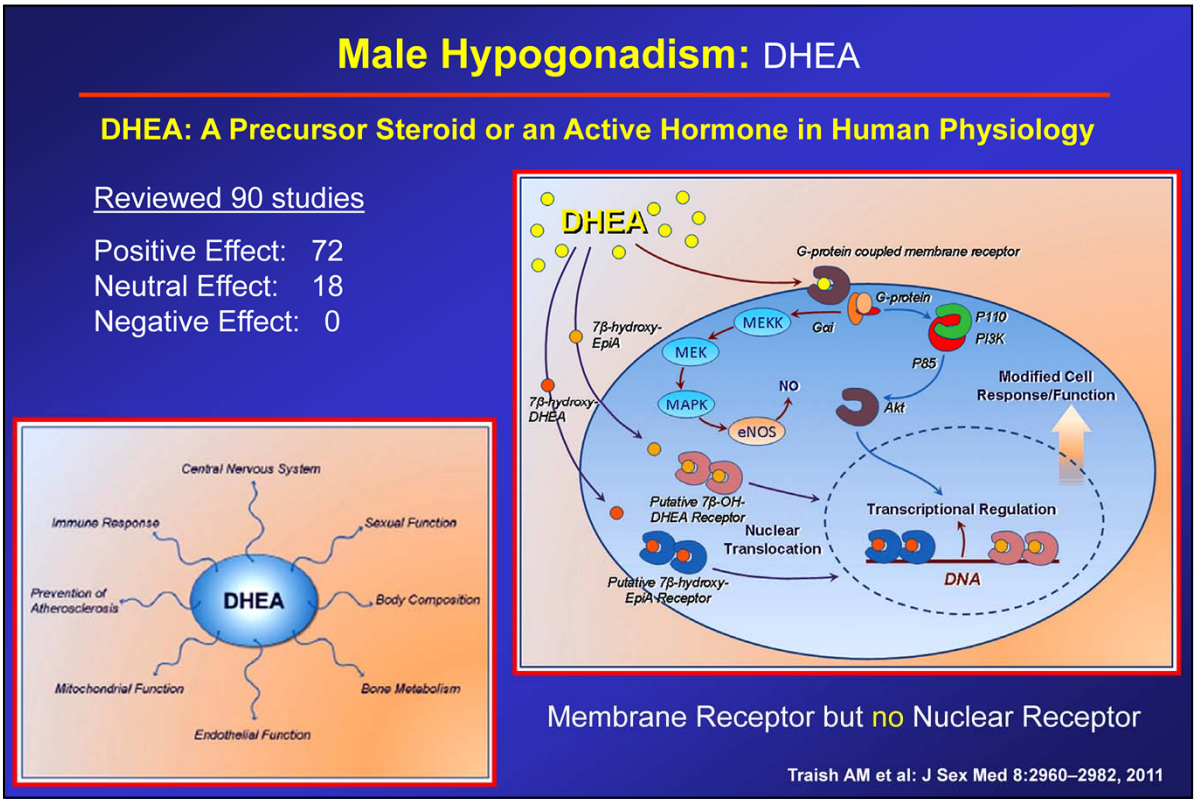
PURPOSE: DHEA therapy increases bone formation in postmenopausal women. We have found only a few reports of dehydroepiandrosterone replacement therapy in women receiving long-term glucocorticoid medication. The purpose of this study was to establish whether DHEA replacement therapy may be useful in the treatment of steroid-induced osteoporosis in postmenopausal women.

MATERIALS AND METHODS: Nineteen women, aged 50-78 years, treated at least for three years with average daily doses of more than 7.5 mg prednisone, with T-score L2/L4<-1.5 and bisphosphonates intolerance, were enrolled to the study. For the first year of the study the patients were given calcium, vitamin D3 and thiazide diuretics. For another year the patients received orally micronized DHEA 25-50 mg daily. Before the study, after twelve months of Calcium/D3 therapy, then after six weeks and six months of DHEA therapy, serum concentrations of DHEAS, androstenedione, testosterone, estradiol, FSH, IGF-1 and osteocalcin were assessed. Bone mineral density (BMD) in lumbar spine and femoral neck was measured before the treatment, after a year on Calcium/D3 and after six and twelve months of DHEA replacement therapy.

RESULTS: In all treated women, DHEA significantly increased serum DHEAS, androstenedione and testosterone concentrations. A significant elevation of serum IGF-1 and osteocalcin concentrations was found as early as after six weeks of

DHEA treatment. A significant increase of bone mineral density in the lumbar spine and femoral neck was observed after six and twelve months of DHEA treatment.

CONCLUSION: Our results suggest a beneficial role of DHEA replacement therapy in the treatment of steroid-induced osteoporosis.



INTRODUCTION: The circulation of large amounts of dehydroepiandrosterone (DHEA) and its sulfated derivative (DHEA-S) suggests a physiological role in human physiology. In the central nervous system, DHEA is considered a neurosteroid with a wide range of functions.

AIM: The goal of this review is to discuss metabolism, biochemical, and physiological mechanism of DHEA action and the potential role of DHEA in aging and in ameliorating a host of pathological conditions, associated with aging.

METHODS: We examined preclinical and clinical data reported in various studies from the available literature concerning the effects of DHEA in normal and pathological conditions.

MAIN OUTCOME MEASURES: Data reported in the literature were analyzed, reviewed, and discussed.

RESULTS: DHEA mediates its action via multiple signaling pathways involving specific membrane receptors and via transformation into androgen and estrogen derivatives (e.g., androgens, estrogens, 7α and 7β DHEA, and 7α and 7β epiandrosterone derivatives) acting through their specific receptors. These

pathways include: nitric oxide synthase activation, modulation of γ-amino butyric acid receptors, N-methyl D-aspartate, receptors sigma receptors (Sigma-1), differential expression of inflammatory factors, adhesion molecules and reactive oxygen species, among others. Clinical and epidemiological studies suggested that low DHEA levels might be associated with ischemic heart disease, endothelial dysfunction, atherosclerosis, bone loss, inflammatory diseases, and sexual dysfunction. Most importantly, no significant adverse or negative side effects of DHEA were reported in clinical studies of men and women.

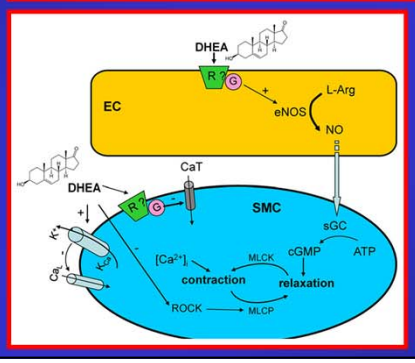
CONCLUSIONS: DHEA modulates endothelial function, reduces inflammation, improves insulin sensitivity, blood flow, cellular immunity, body composition, bone metabolism, sexual function, and physical strength in frailty and provides neuroprotection, improves cognitive function, and memory enhancement. DHEA possesses pleiotropic effects and reduced levels of DHEA and DHEA-S may be associated with a host of pathologies; however, the clinical efficacy of DHEA supplementation in ameliorating patho-physiological symptoms remains to be evaluated.

Male Hypogonadism: DHEA

Role of DHEA in Cardiovascular Diseases

Table 1
Different mechanisms of action of DHEA in cardiovascular system.

Signaling pathways	Tissue/cell type	Pathophysiological role of DHEA
eNos phosphorylation/NO production (+)	EC	Prevention of endothelial dysfunction
Oxidative stress (−)	EC and cardiac cells	Prevention of oxidative injury in cardiovascular system
Akt/GSK-3β/NFAT (−)	EC and VSMC	Anti vascular remodeling effect
Src/STAT3 (−)	PASMC	Anti vascular remodeling effect
Ionic channels		
BK_{Ca} (+)	PASMC	Membrane hyperpolarization, vasorelaxation
T-type Ca channels (−)		Prevention of PH
RhoA/RhoA kinase (−)	PASMC	Prevention of PH
(HIF-1α) (−)	PASMC	Prevention of PH
s/cGMP (+)	PASMC	Prevention of PH
DHEA receptors		
Plasma membrane associated (+)	EC and PASMC	NO production vasorelaxation
Cytosolic/nuclear hormone receptor (+)	EC and VSMC	Anti vascular remodeling effect
Endoplamic reticulum membrane associated receptor: Sigma-1 receptor (+)	Cardiac cell	Protection of cardiac injury and hypertension



May be particularly important in Pulmonary Hypertension

Savineau JP et al: Biochemical Pharmacology 85 (2013) 718–726

Abstract Dehydroepiandrosterone (DHEA) is a steroid hormone derived from cholesterol synthesized by the adrenal glands. DHEA and its 3β-sulphate ester (DHEA-S) are the most abundant circulating steroid hormones. In human, there is a clear age-related decline in serum DHEA and DHEA-S and this has suggested that a relative deficiency in these steroids may be causally related to the development of a series of diseases associated with aging including cardiovascular diseases (CVD). This commentary aims to highlight the action of DHEA in CVD and its beneficial effect in therapy. We thus discuss the possible impact of serum DHEA decline and DHEA supplementation in diseases such as hypertension, coronary artery disease and atherosclerosis. More specifically, we provide evidence for a beneficial action of DHEA in the main disease of the pulmonary circulation: pulmonary hypertension. We also examine the potential cellular mechanism of action of DHEA in terms of receptors (membrane/nuclear) and associated signaling pathways (ion channels, calcium signaling, PI3K/AKT/eNos pathway, cGMP, RhoA/RhoK pathway). We show that DHEA acts as an anti-remodeling and vasorelaxant drug. Since it is a well-tolerated and inexpensive drug, DHEA may prove to be a valuable molecule in CVD but it deserves further studies both at the molecular level and in large clinical trials.

Abstract (Aging Cell 11:876–884, 2012) Serum dehydroepiandrosterone (DHEA) concentrations decrease approximately 80% between ages 25 and 75 year. Aging also results in an increase in arterial stiffness, which is an independent predictor of cardiovascular disease (CVD) risk and mortality. Therefore, it is conceivable that DHEA replacement in older adults could reduce arterial stiffness. We sought to determine whether DHEA replacement therapy in older adults reduces carotid augmentation index (AI) and carotid-femoral pulse wave velocity (PWV) as indices of arterial stiffness. A randomized, double-blind trial was conducted to study the effects of 50 mg day(-1) DHEA replacement on AI (n = 92) and PWV (n = 51) in women and men aged 65-75 year. Inflammatory cytokines and sex hormones were measured in fasting serum. AI decreased in the DHEA group, but not in the placebo group (difference between groups, -6 ± 2 AI units, P = 0.002). Pulse wave velocity also decreased (difference between groups, -3.5 ± 1.0 m s(-1), P = 0.001); however, after adjusting for baseline values, the between-group comparison became nonsignificant (P = 0.20). The reductions in AI and PWV were accompanied by decreases in inflammatory cytokines (tumor necrosis factor α and IL-6, P < 0.05) and correlated with increases in serum DHEAS (r = -0.31 and -0.37, respectively, P < 0.05). The reductions in AI also correlated with free testosterone index (r = -0.23, P = 0.03). In conclusion, DHEA replacement in elderly men and women improves indices of arterial stiffness. Arterial stiffness increases with age and is an independent risk factor for CVD. Therefore, the improvements observed in this study suggest that DHEA replacement might partly reverse arterial aging and reduce CVD risk.

Abstract (Rejuven Res 16:285-294, 2013) Dehydroepiandrosterone (DHEA) and its sulfate ester are the most abundant steroids in humans. DHEA levels fall with age in men and women, reaching values sometimes as low as 10%-20% of those encountered in young individuals. This age-related decrease suggests an "adrenopause" phenomenon. Studies point toward several potential roles of DHEA, mainly through its hormonal end products, making this decline clinically relevant. Unfortunately, even if positive effects of DHEA on muscle, bone, cardiovascular disease, and sexual function seem rather robust, extremely few studies are large enough and/or long enough for conclusions regarding its effects on aging. Moreover, because it has been publically presented as a "fountain of youth" equivalent, over-the-counter preparations lacking pharmacokinetic and pharmacodynamic data are widely used worldwide. Conceptually, supplementing a pre-hormone is extremely interesting, because it would permit the human organism to adequately use it throughout long periods, increasing or decreasing end products according to his needs. Nevertheless, data on the safety profile of long-term DHEA supplementation are still lacking. In this article, we examine the potential relation between low DHEA levels and well-known age-related diseases, such as sarcopenia, osteoporosis, dementia, sexual disorders, and cardiovascular disease. We also review risks and benefits of existing protocols of DHEA supplementation.

Abstract (Adv Med Sci 57:51-57, 2012)

PURPOSE: DHEA therapy increases bone formation in postmenopausal women. We have found only a few reports of dehydroepiandrosterone replacement therapy in women receiving long-term glucocorticoid medication. The purpose of this study was to establish whether DHEA replacement therapy may be useful in the treatment of steroid-induced osteoporosis in postmenopausal women.

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CONCLUSION: Our results suggest a beneficial role of DHEA replacement therapy in the treatment of steroid-induced osteoporosis.

Abstract (JAMA 292:2243-8, 2004)

CONTEXT: Dehydroepiandrosterone (DHEA) administration has been shown to reduce accumulation of abdominal visceral fat and protect against insulin resistance in laboratory animals, but it is not known whether DHEA decreases abdominal obesity in humans. DHEA is widely available as a dietary supplement without a prescription.

OBJECTIVE: To determine whether DHEA replacement therapy decreases abdominal fat and improves insulin action in elderly persons.

DESIGN AND SETTING: Randomized, double-blind, placebo-controlled trial conducted in a US university-based research center from June 2001 to February 2004.

PARTICIPANTS: Fifty-six elderly persons (28 women and 28 men aged 71 [range, 65-78] years) with age-related decrease in DHEA level.

INTERVENTION: Participants were randomly assigned to receive 50 mg/d of DHEA or matching placebo for 6 months.

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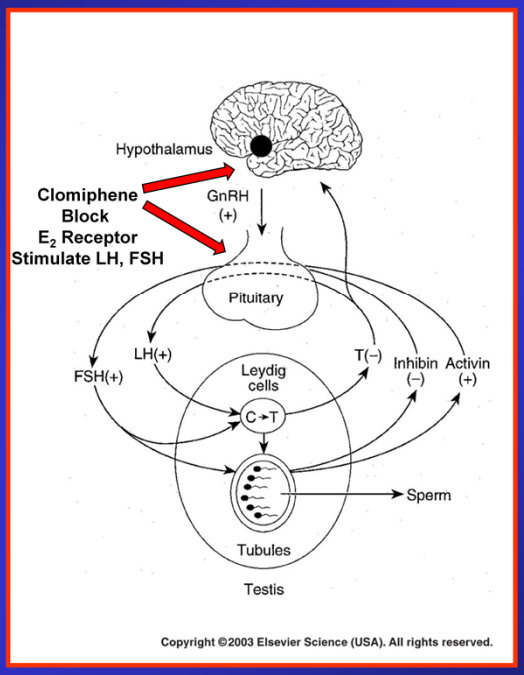
Compliance with the intervention was 97% in the DHEA group and 95% in the placebo group. Based on intention-to-treat analyses, DHEA therapy compared with placebo induced significant decreases in visceral fat area (-13 cm2 vs +3 cm2, respectively; P = .001) and subcutaneous fat (-13 cm2 vs +2 cm2, P = .003). The insulin area under the curve (AUC) during the OGTT was significantly reduced after 6 months of DHEA therapy compared with placebo (-1119 muU/mL per 2 hours vs +818 muU/mL per 2 hours, P = .007). Despite the lower insulin levels, the glucose AUC was unchanged, resulting in a significant increase in an insulin sensitivity index in response to DHEA compared with placebo (+1.4 vs -0.7, P = .005).

CONCLUSION: DHEA replacement could play a role in prevention and treatment of the metabolic syndrome associated with abdominal obesity.

Male Hypogonadism – Clomiphene (SERM)



Male Hypogonadism: Clomiphene

Enclomiphene stimulates testosterone production while preventing oligospermia: randomized phase II trial comparing topical testosterone

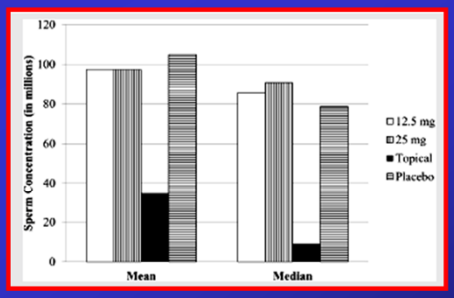
Pure E_2 antagonist - Half-life 10.5 hrs v 30 days for ZuC
Age ~50 BMI ~32 ~30 subj/group ~60% completed
Doses: 12.5, 25 mg vs topical testosterone for 3 mths

No difference between doses (only 25 mg shown)

	Testosterone (ng/dl):	Estradiol (pg/dl):
EC:	210 → 406	25 → 46*
T T:	210 → 463	26 → 38*
Plac:	214 → 199	22 → 24

	SHBG (nmol/L):	DHT (ng/dl):
EC:	26 → 30	15 → 23*
T T:	26 → 25	15 → 52**
Plac:	28 → 31	14 → 16

	LH (mIU/ml):	FSH (mIU/ml):
EC:	5.3 → 11.7	9.4 → 14.9
T T:	3.9 → 1.4	6.0 → 2.4
Plac:	3.9 → 3.7	6.1 → 5.4



Low LH & Sperm Count:		
EC:	0/30	0/19
T T:	17/31	10/19
Plac:	4/24	2/13

Wiehle RD et al: Fertil Steril 102:720–7, 2014

OBJECTIVE: To determine the effect of enclomiphene citrate in men with secondary hypogonadism.

DESIGN: Phase II clinical trial.

SETTING: Community dwelling men making visits to physician offices.

PATIENT(S): Men with secondary hypogonadism.

INTERVENTION(S): Oral administration of enclomiphene citrate or 1% topical T gel.

MAIN OUTCOME MEASURE(S): Luteinizing hormone, FSH, T, and semen analysis.

RESULT(S): Treatment with enclomiphene citrate resulted in increased morning serum T, E2, and LH levels similar to those obtained with a topical T gel in men with secondary hypogonadism. Follicle-stimulating hormone and LH were increased with enclomiphene, and sperm counts were conserved.

CONCLUSION(S): Enclomiphene citrate reverses the two hallmarks of secondary hypogonadism, namely, low serum total T and low or inappropriately normal LH while preserving sperm production.

Male Hypogonadism: Clomiphene

Predicting Biochemical Response to Clomiphene in Hypogonadal Men
76 men taking between 100 to 350 mg weekly for 6-11 months

Table 1 Patients' characteristics

Characteristic	
Age, mean ± SD (range), years	46 ± 22 (21–67)
Hypertension (%)	27
Hyperlipidemia (%)	33
Smoking (%)	19
Diabetes (%)	12
Varicocele grade II or III (%)	18.4
Unilateral (%)	11.8
Bilateral (%)	6.6
Testicular volume (mL)	16 ± 8

64% Response Rate:

>200 ng/dl increase &
Serum level >400 ng/dl

Table 2 Hormone outcomes

	Baseline	Treatment	*P* value
Mean total T (ng/dL)	179 ± 72	467 ± 190	<0.01
Mean free T (pg/mL)	26 ± 19	76 ± 54	<0.01
Mean E2 (pg/mL)	29 ± 31	42 ± 20	<0.01
Mean LH (IU/mL)	5.2 ± 5.6	10.8 ± 3.8	<0.01

E2 = estradiol 2; LH = luteinizing hormone; T = testosterone

Table 3 Multivariable analysis of predictors of successful biochemical response to clomiphene citrate

Factors			
Continuous variables	adj. *r*		*P* value
Mean testicular volume	0.32		<0.01
LH level	0.48		<0.001
Dichotomous variables	HR	95% CI	*P* value
Testicular volume ≥14 mL	2.2	1.4–5.2	<0.01
LH level ≤6 IU/mL	3.5	1.9–7.8	<0.001

adj. *r* = adjusted ratio; CI = confidence interval; LH = luteinizing hormone; HR = hazard ratio

Mazzola CR: J Sex Med 11:2302–2307, 2014

INTRODUCTION: Clomiphene citrate (CC) is as an effective treatment for men with hypogonadism (HG). Identifying the ideal candidate for this strategy has to date largely relied upon a patient's interest in preservation of testicular volume and spermatogenesis.

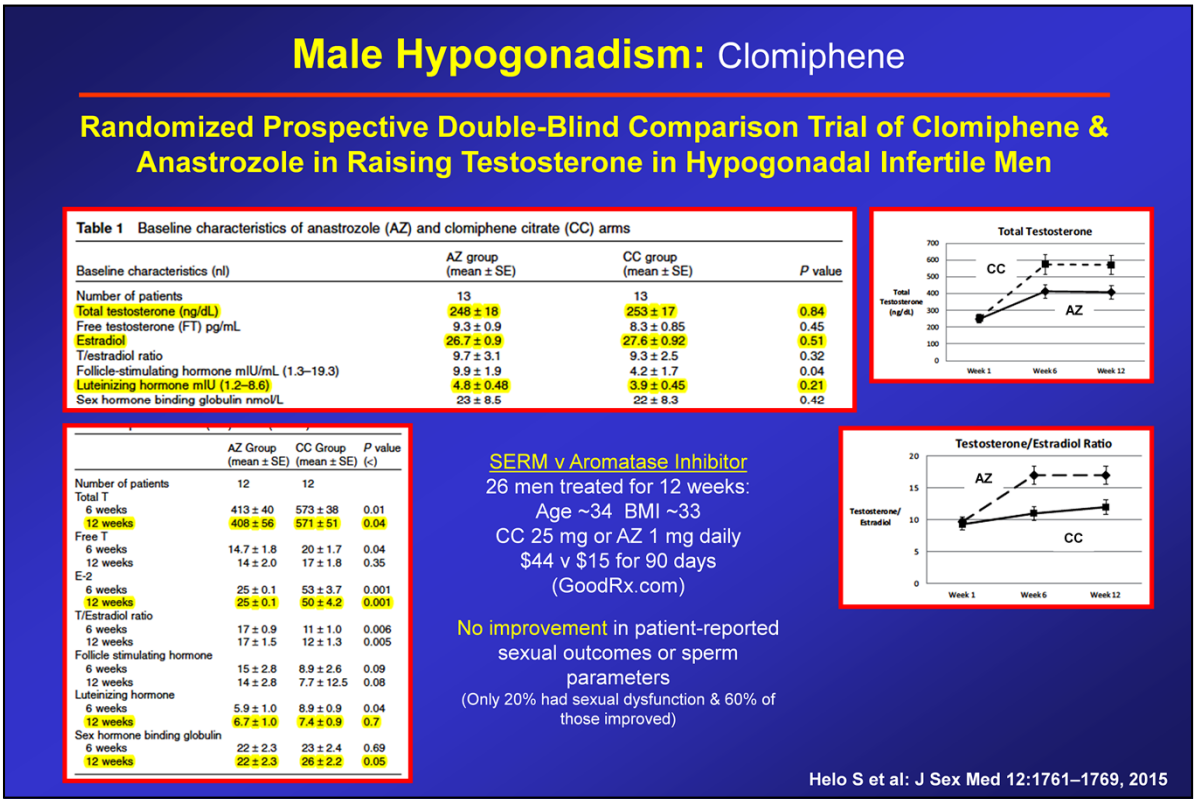
AIM: This analysis was undertaken to define if predictors existed of robust elevation in serum testosterone (T) levels in response to CC.

METHODS: Seventy-six men with a diagnosis of HG (two separate early morning total T levels <300 ng/dL) opting for CC therapy constituted the study population. Demographic, comorbidity data, and physical and laboratory characteristics were recorded. Laboratory tests were conducted 4 weeks after commencement and every 6 months thereafter. Multivariable analysis was conducted to define if predictors of biochemical response could be identified. Parameters included in the model were patient age, mean testicular volume, varicocele presence, and baseline total T, free T, and luteinizing hormone (LH) levels.

MAIN OUTCOME MEASURE: Successful biochemical response to CC, defined as an increase of ≥200 ng/dL in total T level at ≥6 months after commencing CC, was the main outcome measure.

RESULTS: Mean age was 46 ± 22 years. Mean pretreatment testicular volume was 16 ± 8 mL. Mean baseline T and LH levels were 179 ± 72 ng/dL and 7.2 ± 5.6 IU/mL, respectively. Mean total T on CC was 467 ± 190 ng/dL. Forty-seven patients (62%) met the responder definition, with a mean increase in total T levels of 302 ± 76 (204-464) ng/dL. In CC responders, the mean LH rise was 5.6 ± 3.1 IU/mL. On multivariable analysis, factors predictive of CC response included: mean testicular volume (adjusted [adj.] $r = 0.32$, $P < 0.01$), mean testicular volume ≥14 mL (hazard ratio [HR] 2.2, $P < 0.01$), LH level (adj. $r = 0.48$, $P < 0.001$), and LH level ≤6 IU/mL (HR 3.5, $P < 0.001$).

CONCLUSION: These data indicate that two thirds of men with HG meet a robust responder definition and that pretreatment testicular volume and LH levels (in continuous and dichotomized fashions) are predictors of response.



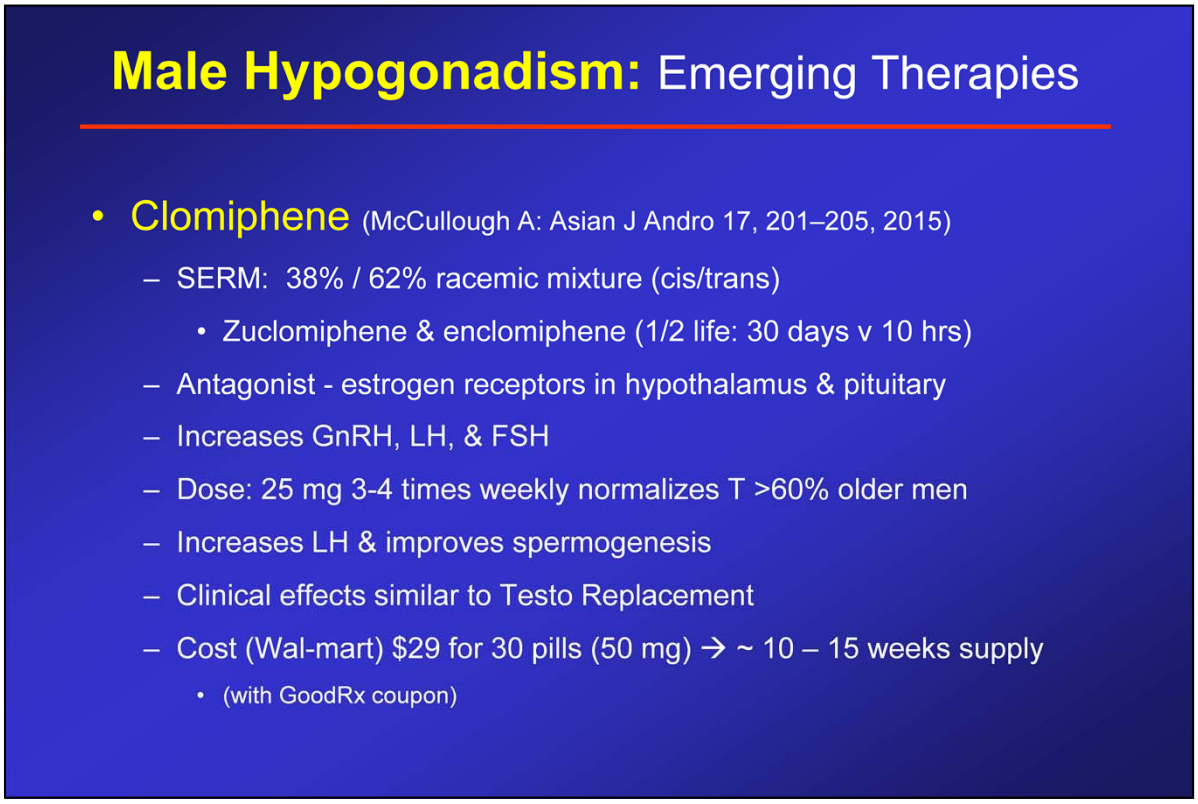
AIM: Clomiphene citrate (CC) and anastrozole (AZ) have been used off label to increase testosterone (T) in hypogonadal infertile men (HIM). Both medications have been shown to increase T with different effects on estradiol (E2) and T-to-E2 ratios. There are no reported randomized trials comparing CC and AZ to improve T levels in HIM. We aimed to establish equivalence of CC vs. AZ with respect to improvement in T levels in HIM.

METHODS: We randomized 26 HIM (T less than 350 ng/dL and normal luteinizing hormone [LH]). Patients were randomized to CC (25 mg/day) or AZ (1 mg/day) for 12 weeks. Hormones assayed were total T, free T, E2, LH, follicle stimulating hormone (FSH), and sex hormone binding globulin (SHBG). Patient-reported outcomes were the International Index of Erectile Function, Erection Hardness Scale, and the Androgen Deficiency in the Aging Male questionnaires. Blood tests and questionnaires were recorded at baseline, 6 and 12 weeks. Semen analyses were performed at baseline and 12 weeks.

RESULTS: T increased significantly from baseline in both groups at 6 and 12 weeks. There was a significantly larger increase in T and mean increase from baseline in CC vs. AZ (571 vs. 408 ng/dL, respectively). Whereas E-2 levels increased in the CC group, they decreased in the AZ group. Though both groups demonstrated an increase in T-to-E-2 ratio from baseline, statistic significance at 6

and 12 weeks was only achieved with AZ. Neither group demonstrated significant changes in seminal parameters or patient-reported outcomes.

CONCLUSIONS: We failed to demonstrate equivalence of CC vs. AZ. CC resulted in significantly higher T levels than AZ. AZ resulted in a significantly larger increase in T/E-2 ratio than CC. No significant differences between CC and AZ on seminal parameters or patient-reported outcomes were demonstrated.



Abstract The European Male Aging Study has demonstrated that the hypogonadism of male aging is predominantly secondary. Theoretically with appropriate stimulation from the pituitary, the aging testis should be able to produce eugonadal levels of testosterone. The strategies for the treatment of late onset hypogonadism (LOH) have focused on replacement with exogenous testosterone versus restoration of endogenous production. The purpose of this article is to review existing peer-reviewed literature supporting the concept of restoration of endogenous testosterone in the treatment of LOH.

Male Hypogonadism: Testosterone Formulas

- Compounded Testosterone:
  - Rx Compound Center 6 grams in 30 ml Lotion (3-4 months) → ~$90
- IM Testosterone Cyprio: 1 ml, 200 mg/ml, 4 vials → $15/month (Kroger)
- Gel 1.62% Pump (generic): 1 bottle per month → $60/month (Walmart)
- Gel 1% Packets (50 mg): 30 Packets per month → $47/month (Kroger)
- GoodRx.com prices for pharmaceutical supplements with coupon