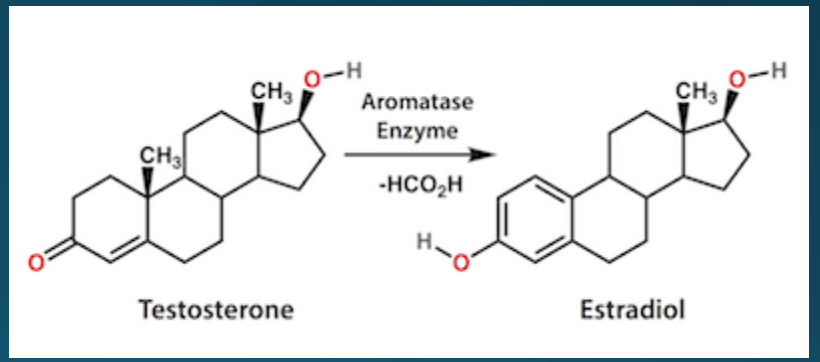
Estrogen in Men Good, Bad or Indifferent?

An evidence-based review for optimal health



NEAL ROUZIER, M.D.

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MANTRA

IT'S FAR BETTER TO WALK ALONE THAN WITH A CROWD THAT'S GOING IN THE WRONG DIRECTION.

WHERE WOULD YOU LIKE YOUR LEVELS OF ESTRADIOL TO BE?

Dear Neal:

I have attended four of your courses and listened to your You-Tube presentations regarding not blocking the aromatization of testosterone to estradiol.

Of course as you have noted there is always an 'argument' or disbelief regarding this. You point out that no study has shown any negative effect of raising estrogen in men and you point out all the benefits. Yet I hear their mutters of disagreement or doubt from doctors.

An article was published by William Faloon in the June 2015 of Life Extension titled "Surprising Factor Behind Sudden Cardiac Arrest." As I am sure you are aware Mr. Faloon makes a strong case for keeping estradiol levels in the range of 20 to 30pg/ml.

Patients bring this article to my attention when I attempt to stop their use of an aromatase inhibitor.

So my questions to you are...

#1 how did this figure become so fixed if there are/were no studies and why is it being promulgated by such an influential source as Life Extension?

#2 What literature supports your view so that I can convince my patients, and you can convince your students, that they should not use blocking agents?

I did follow your advice to stop the anastrazole and my HDL went from 29 to 46.
Sincerely, Jay

Prospective case-control study of premenopausal serum estradiol and testosterone levels and breast cancer risk.

Prospective case-control study of premenop... [Breast Cancer Res. 2... http://www.ncbi.nlm.nih.gov/pubmed/21087481

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Breast Cancer Res. 2010;12(6):R98. Epub 2010 Nov 18.

Prospective case-control study of premenopausal serum estradiol and testosterone levels and breast cancer risk.

Dorgan JF, Stanczyk FZ, Kahle LL, Brinton LA.

Fox Chase Cancer Center, hiladelphia, PA 19111, USA. joanne.dorgan@fccc.edu

Abstract

INTRODUCTION: Breast cancer is frequently a hormonally dependent cancer, and associations of circulating estrogens and androgens with subsequent breast cancer risk are well established in postmenopausal women. Associations of serum estrogens and androgens with breast cancer risk in premenopausal women are less well studied. The objective of this study was to determine whether estradiol and testosterone levels in serum collected before menopause are associated with subsequent breast cancer risk.

METHODS: We conducted a prospective case-control study of 266 participants who were registered in the Columbia, Missouri, Serum Bank and not using exogenous hormones at the time of blood collection. Each of 98 in situ or invasive breast cancer cases with prediagnostic serum collected before menopause was matched to two controls by age, date, menstrual cycle day, and time of day of blood collection. Estradiol and testosterone concentrations were quantified by using specific radioimmunoassays, and sex hormone-binding globulin (SHBG) was quantified with a chemiluminescent immunoassay to allow calculation of the non-SHBG bound hormone fractions. Data were analyzed by using conditional logistic regression. All tests of statistical significance were two-sided.

RESULTS: Serum testosterone was strongly and significantly associated with breast cancer risk. The relative odds (OR) for increasing quartiles of total testosterone were 1.0, 2.1 (95% confidence interval (CI) 0.9 to 4.8), 1.5 (95% CI, 0.6 to 3.4), and 3.3 (95% CI, 1.5 to 7.5, P(trend) = 0.006). Comparable ORs for the non-SHBG bound fraction of testosterone that is bioavailable were 1.0, 1.7 (95% CI, 0.7 to 4.2), 1.7 (95% CI, 0.7 to 4.0), and 4.2 (95% CI, 1.6 to 10.9, P(trend) = 0.002). Total and non-SHBG-bound estradiol were not associated with breast cancer, but extreme variation in levels across the menstrual cycle coupled with relatively small numbers, particularly for analyses stratified by cycle phase, limited the power to detect associations.

CONCLUSIONS: Results suggest that premenopausal women with elevated serum testosterone levels are at an increased risk of breast cancer.

PMID: 21087481 [PubMed - indexed for MEDLINE] PMCID: PMC3046441

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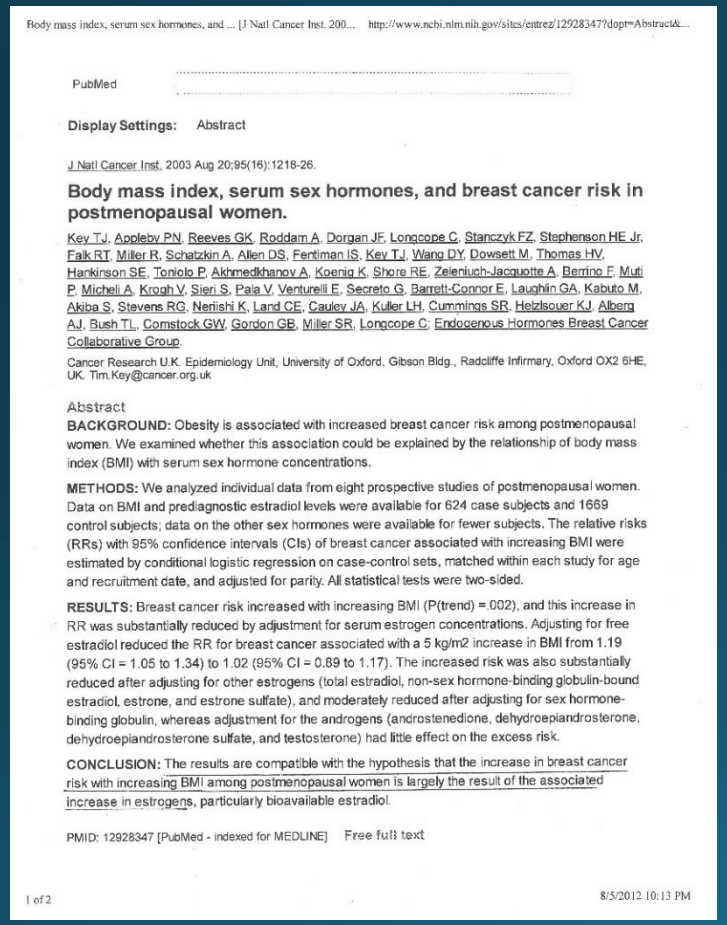
1 of 2 2/7/2012 10:18 PM

- Results suggest that premenopausal women with elevated serum testosterone levels are at an increased risk of breast cancer.

Dorgan JF, Stanczyk FZ, Kahle LL, Brinton LA. Prospective case-control study of premenopausal serum estradiol and testosterone levels and breast cancer risk. *Breast Cancer Res*. 2010;12(6):R98.

Body mass index, serum sex hormones, and breast cancer risk in postmenopausal women.



Body mass index, serum sex hormones, and ... [J Natl Cancer Inst. 200... http://www.ncbi.nlm.nih.gov/sites/entrez/12928347?dopt=Abstract&...

PubMed

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J Natl Cancer Inst. 2003 Aug 20;95(16):1218-26.

Body mass index, serum sex hormones, and breast cancer risk in postmenopausal women.

Key TJ, Appleby PN, Reeves GK, Roddam A, Dorgan JF, Longcope C, Stanczyk FZ, Stephenson HE Jr, Falk RT, Miller R, Schatzkin A, Allen DS, Fentiman IS, Key TJ, Wang DY, Dowsett M, Thomas HV, Hankinson SE, Toniolo P, Akhmedkhanov A, Koenig K, Shore RE, Zeleniuch-Jacquotte A, Berrino F, Muti P, Micheli A, Krogh V, Sieri S, Pala V, Venturelli E, Secreto G, Barrett-Connor E, Laughlin GA, Kabuto M, Akiba S, Stevens RG, Neriishi K, Land CE, Cauley JA, Kuller LH, Cummings SR, Helzlsouer KJ, Alberg AJ, Bush TL, Comstock GW, Gordon GB, Miller SR, Longcope C; Endogenous Hormones Breast Cancer Collaborative Group.

Cancer Research U.K. Epidemiology Unit, University of Oxford, Gibson Bldg., Radcliffe Infirmary, Oxford OX2 6HE, UK. Tim.Key@cancer.org.uk

Abstract

BACKGROUND: Obesity is associated with increased breast cancer risk among postmenopausal women. We examined whether this association could be explained by the relationship of body mass index (BMI) with serum sex hormone concentrations.

METHODS: We analyzed individual data from eight prospective studies of postmenopausal women. Data on BMI and prediagnostic estradiol levels were available for 624 case subjects and 1669 control subjects; data on the other sex hormones were available for fewer subjects. The relative risks (RRs) with 95% confidence intervals (CIs) of breast cancer associated with increasing BMI were estimated by conditional logistic regression on case-control sets, matched within each study for age and recruitment date, and adjusted for parity. All statistical tests were two-sided.

RESULTS: Breast cancer risk increased with increasing BMI (P(trend) = .002), and this increase in RR was substantially reduced by adjustment for serum estrogen concentrations. Adjusting for free estradiol reduced the RR for breast cancer associated with a 5 kg/m2 increase in BMI from 1.19 (95% CI = 1.05 to 1.34) to 1.02 (95% CI = 0.89 to 1.17). The increased risk was also substantially reduced after adjusting for other estrogens (total estradiol, non-sex hormone-binding globulin-bound estradiol, estrone, and estrone sulfate), and moderately reduced after adjusting for sex hormone-binding globulin, whereas adjustment for the androgens (androstenedione, dehydroepiandrosterone, dehydroepiandrosterone sulfate, and testosterone) had little effect on the excess risk.

CONCLUSION: The results are compatible with the hypothesis that the increase in breast cancer risk with increasing BMI among postmenopausal women is largely the result of the associated increase in estrogens, particularly bioavailable estradiol.

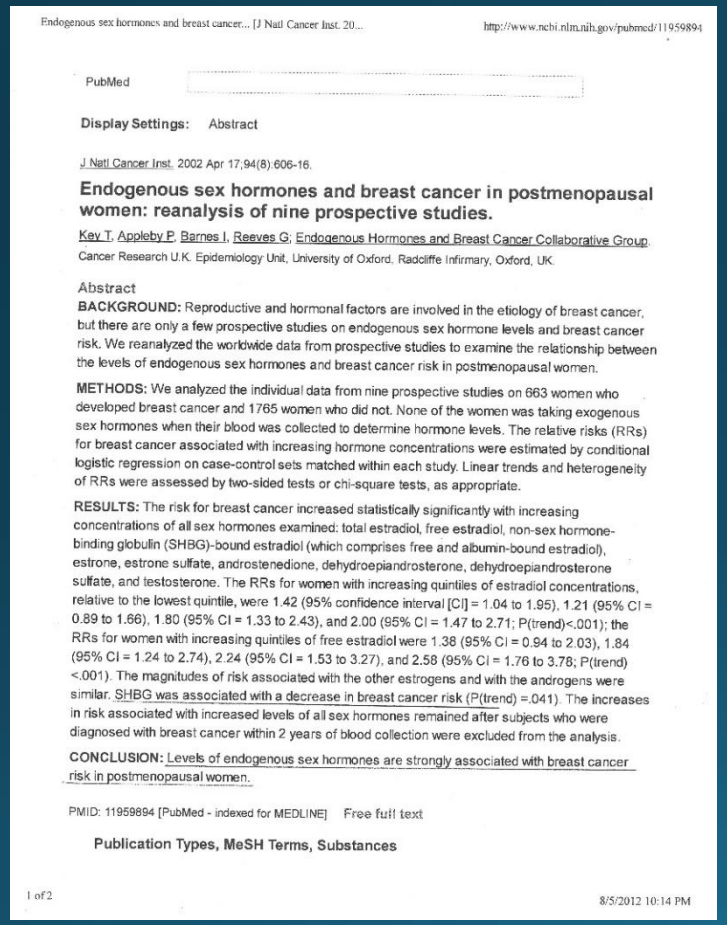
PMID: 12928347 [PubMed - indexed for MEDLINE] Free full text

1 of 2 8/5/2012 10:13 PM

- The results are compatible with the hypothesis that the increase in breast cancer risk with increasing BMI among postmenopausal women is largely the results of the associated increase in estrogens.

Key TJ, Appleby PN, Reeves GK, et al. Body mass index, serum sex hormones, and breast cancer risk in postmenopausal women. *J Natl Cancer Inst*. 2003 Aug 20;95(16):1218-26.

Endogenous sex hormones and breast cancer in postmenopausal women: reanalysis of nine prospective studies.



Endogenous sex hormones and breast cancer... [J Natl Cancer Inst. 20... http://www.ncbi.nlm.nih.gov/pubmed/11959894

PubMed

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J Natl Cancer Inst. 2002 Apr 17;94(8):606-16.

Endogenous sex hormones and breast cancer in postmenopausal women: reanalysis of nine prospective studies.

Key T, Appleby P, Barnes I, Reeves G; Endogenous Hormones and Breast Cancer Collaborative Group.
Cancer Research U.K. Epidemiology Unit, University of Oxford, Radcliffe Infirmary, Oxford, UK.

Abstract

BACKGROUND: Reproductive and hormonal factors are involved in the etiology of breast cancer, but there are only a few prospective studies on endogenous sex hormone levels and breast cancer risk. We reanalyzed the worldwide data from prospective studies to examine the relationship between the levels of endogenous sex hormones and breast cancer risk in postmenopausal women.

METHODS: We analyzed the individual data from nine prospective studies on 663 women who developed breast cancer and 1765 women who did not. None of the women was taking exogenous sex hormones when their blood was collected to determine hormone levels. The relative risks (RRs) for breast cancer associated with increasing hormone concentrations were estimated by conditional logistic regression on case-control sets matched within each study. Linear trends and heterogeneity of RRs were assessed by two-sided tests or chi-square tests, as appropriate.

RESULTS: The risk for breast cancer increased statistically significantly with increasing concentrations of all sex hormones examined: total estradiol, free estradiol, non-sex hormone-binding globulin (SHBG)-bound estradiol (which comprises free and albumin-bound estradiol), estrone, estrone sulfate, androstenedione, dehydroepiandrosterone, dehydroepiandrosterone sulfate, and testosterone. The RRs for women with increasing quintiles of estradiol concentrations, relative to the lowest quintile, were 1.42 (95% confidence interval [CI] = 1.04 to 1.95), 1.21 (95% CI = 0.89 to 1.66), 1.80 (95% CI = 1.33 to 2.43), and 2.00 (95% CI = 1.47 to 2.71; P(trend)<.001); the RRs for women with increasing quintiles of free estradiol were 1.38 (95% CI = 0.94 to 2.03), 1.84 (95% CI = 1.24 to 2.74), 2.24 (95% CI = 1.53 to 3.27), and 2.58 (95% CI = 1.76 to 3.78; P(trend) <.001). The magnitudes of risk associated with the other estrogens and with the androgens were similar. SHBG was associated with a decrease in breast cancer risk (P(trend) =.041). The increases in risk associated with increased levels of all sex hormones remained after subjects who were diagnosed with breast cancer within 2 years of blood collection were excluded from the analysis.

CONCLUSION: Levels of endogenous sex hormones are strongly associated with breast cancer risk in postmenopausal women.

PMID: 11959894 [PubMed - indexed for MEDLINE] Free full text

Publication Types, MeSH Terms, Substances

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- Levels of endogenous sex hormones are strongly associated with breast cancer risk in postmenopausal women.

Key T, Appleby P, Barnes I, et al. Endogenous sex hormones and breast cancer in postmenopausal women: reanalysis of nine prospective studies. *J Natl Cancer Inst*. 2002 Apr 17;94(8):606-16.

Serum concentrations of estrogens, sex hormone-binding globulin, and androgens and risk of breast cancer in postmenopausal women.

Serum concentrations of estrogens, sex hormone-... [Int J Cancer. 2006... http://www.ncbi.nlm.nih.gov/sites/entrez/16894564?dopt=Abstract&...

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Full Text Online

Int J Cancer. 2006 Nov 15;119(10):2402-7.

Serum concentrations of estrogens, sex hormone-binding globulin, and androgens and risk of breast cancer in postmenopausal women.

Adly L, Hill D, Sherman ME, Sturgeon SR, Fears T, Mies C, Ziegler RG, Hoover RN, Schairer C.

Department of Epidemiology and Biostatistics, School of Public Health and Health Services, George Washington University, Washington, DC, USA.

Abstract

We assessed the relationship between serum concentrations of estrogens, androgens, and sex hormone-binding globulin and risk of breast cancer among postmenopausal women. Study participants provided serum prior to breast biopsy or mastectomy in 3 hospitals in Grand Rapids, Michigan between 1977 and 1987. A total of 179 subjects with localized breast cancer were compared to 152 subjects with nonproliferative breast changes that have not been associated with elevated breast cancer risk. Increasing serum concentrations of estrone and estrone sulfate were associated with increases in breast cancer risk; the odds ratios (ORs) in the fourth quartiles compared to the first were 2.3 (95% confidence interval (CI) 1.1-4.6) for both (p-trend = 0.02 and 0.03, respectively). Estradiol and bioavailable estradiol concentrations were associated with nonstatistically significant increases in risk. Androstenediol levels were associated with risk (p-trend = 0.01); the OR in the fourth compared to the first quartile was 2.2 (95% CI 1.0-4.6). Testosterone, dehydroepiandrosterone and androstenedione levels were not associated with increased risk. Sex hormone-binding globulin was associated with a nonsignificant decrease in risk. Associations with estrone and estrone sulfate persisted after adjustment for androstenediol (ORs for fourth compared to first quartiles were 2.0 (95% CI 0.9-4.5) and 2.2 (95% CI 1.0-4.6), respectively (p-trend = 0.16 for both). The association with androstenediol was attenuated after adjustment for estrone (OR for fourth compared to first quartile was 1.6 (95% CI 0.7-3.6); p-trend = 0.13). Higher serum concentrations of estrogens were associated with increased breast cancer risk in postmenopausal women. Androgen levels were not independently associated with substantially increased risk.

PMID: 16894564 [PubMed - indexed for MEDLINE]

Publication Types, MeSH Terms, Substances

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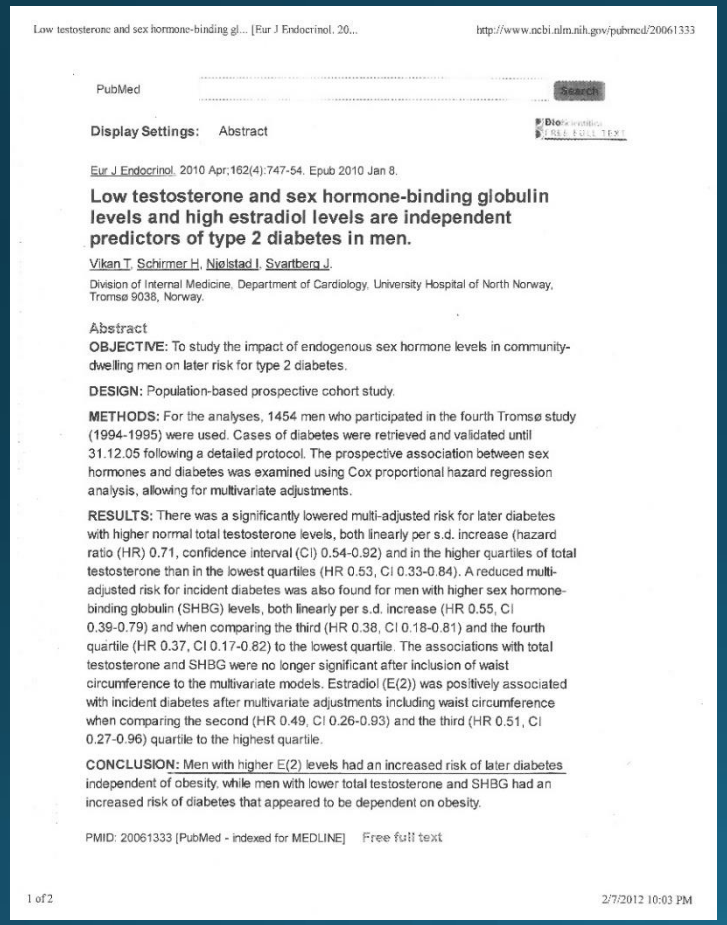
- Higher serum concentrations of estrogens were associated with increased breast cancer risk in postmenopausal women.

Low testosterone and sex hormone-binding globulin levels and high estradiol levels are independent predictors of type 2 diabetes in men.



Low testosterone and sex hormone-binding gl... [Eur J Endocrinol. 20... http://www.ncbi.nlm.nih.gov/pubmed/20061333

PubMed Search

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Eur J Endocrinol. 2010 Apr;162(4):747-54. Epub 2010 Jan 8.

Low testosterone and sex hormone-binding globulin levels and high estradiol levels are independent predictors of type 2 diabetes in men.

Vikan T, Schirmer H, Njølstad I, Svartberg J.

Division of Internal Medicine, Department of Cardiology, University Hospital of North Norway, Tromsø 9038, Norway.

Abstract

OBJECTIVE: To study the impact of endogenous sex hormone levels in community-dwelling men on later risk for type 2 diabetes.

DESIGN: Population-based prospective cohort study.

METHODS: For the analyses, 1454 men who participated in the fourth Tromsø study (1994-1995) were used. Cases of diabetes were retrieved and validated until 31.12.05 following a detailed protocol. The prospective association between sex hormones and diabetes was examined using Cox proportional hazard regression analysis, allowing for multivariate adjustments.

RESULTS: There was a significantly lowered multi-adjusted risk for later diabetes with higher normal total testosterone levels, both linearly per s.d. increase (hazard ratio (HR) 0.71, confidence interval (CI) 0.54-0.92) and in the higher quartiles of total testosterone than in the lowest quartiles (HR 0.53, CI 0.33-0.84). A reduced multi-adjusted risk for incident diabetes was also found for men with higher sex hormone-binding globulin (SHBG) levels, both linearly per s.d. increase (HR 0.55, CI 0.39-0.79) and when comparing the third (HR 0.38, CI 0.18-0.81) and the fourth quartile (HR 0.37, CI 0.17-0.82) to the lowest quartile. The associations with total testosterone and SHBG were no longer significant after inclusion of waist circumference to the multivariate models. Estradiol (E(2)) was positively associated with incident diabetes after multivariate adjustments including waist circumference when comparing the second (HR 0.49, CI 0.26-0.93) and the third (HR 0.51, CI 0.27-0.96) quartile to the highest quartile.

CONCLUSION: Men with higher E(2) levels had an increased risk of later diabetes independent of obesity, while men with lower total testosterone and SHBG had an increased risk of diabetes that appeared to be dependent on obesity.

PMID: 20061333 [PubMed - indexed for MEDLINE] Free full text

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- Men with higher estradiol levels had an increased risk of diabetes.

Vikan T, Schirmer H, Njølstad I, Svartberg J. Low testosterone and sex hormone-binding globulin levels and high estradiol levels are independent predictors of type 2 diabetes in men. *Eur J Endocrinol.* 2010 Apr;162(4):747-54.

Circulating Estradiol and Mortality in Men With Systolic Chronic Heart Failure

American Pharmacists Association | Article http://japha.org/article.aspx?articleid=1472

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May-June 2009, Vol. 301, No. 18 >

Original Contribution

Circulating Estradiol and Mortality in Men With Systolic Chronic Heart Failure

Ewa A. Jankowska, MD, PhD; Piotr Rozentryt, MD, PhD; Beata Ponikowska, MD, PhD; Oliver Hartmann; Dorota Kustrzycka-Kratochwil, PhD; Krzysztof Reczuch, MD, PhD; Jolanta Nowak, MD, PhD; Ludmila Borodulin-Nadzieja, PhD; Lech Polonski, MD, PhD; Waldemar Banasiak, MD, PhD; Philip A. Poole-Wilson, MD, FMedSci; Stefan D. Anker, MD, PhD; Piotr Ponikowski, MD, PhD

JAMA 2009;301:1892-1901. doi:10.1001/jama.2009.639

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Abstract

Context

Androgen deficiency is common in men with chronic heart failure (HF) and is associated with increased morbidity and mortality. Estrogens are formed by the aromatization of androgens; therefore, abnormal estrogen metabolism would be anticipated in HF.

Objective

To examine the relationship between serum concentration of estradiol and mortality in men with chronic HF and reduced left ventricular ejection fraction (LVEF).

Design, Setting, and Participants

A prospective observational study at 2 tertiary cardiology centers (Wroclaw and Zabrze, Poland) of 501 men (mean [SD] age, 58 [12] years) with chronic HF, LVEF of 28% (SD, 8%), and New York Heart Association (NYHA) classes 1, 2, 3, and 4 of 52, 231, 181, and 37, respectively, who were recruited between January 1, 2002, and May 31, 2006. Cohort was divided into quintiles of serum estradiol (quintile 1, <12.90 pg/mL; quintile 2, 12.90-21.79 pg/mL; quintile 3, 21.80-30.11 pg/mL; quintile 4, 30.12-37.39 pg/mL; and quintile 5, ≥37.40 pg/mL). Quintile 3 was considered prospectively as the reference group.

Main Outcome Measures

Serum concentrations of estradiol and androgens (total testosterone and dehydroepiandrosterone sulfate [DHEA-S]) were measured using immunoassays.

Results

Among 501 men with chronic HF, 171 deaths (34%) occurred during the 3-year follow-up. Compared with quintile 3, men in the lowest and highest estradiol quintiles had increased mortality (adjusted hazard ratio [HR], 4.17; 95% confidence interval [CI], 2.33-7.45 and HR, 2.33; 95% CI, 1.30-4.18; respectively; $P < .001$). These 2 quintiles had different clinical characteristics (quintile 1: increased serum total testosterone, decreased serum DHEA-S, advanced NYHA class, impaired renal function, and decreased total fat tissue mass; and quintile 5: increased serum bilirubin and liver enzymes, and decreased serum sodium; all $P < .05$ vs quintile 3). For increasing estradiol quintiles, 3-year survival rates adjusted for clinical variables and androgens were 44.6% (95% CI, 24.4%-63.0%), 65.8% (95% CI, 47.3%-79.2%), 82.4% (95% CI, 69.4%-90.2%), 79.0% (95% CI, 65.5%-87.6%), and 63.6% (95% CI, 46.6%-76.5%); respectively ($P < .001$).

Conclusion

Among men with chronic HF and reduced LVEF, high and low concentrations of estradiol compared with the middle quintile of estradiol are related to an increased mortality.

JAMA. 2009; 301(18); 1892-1901

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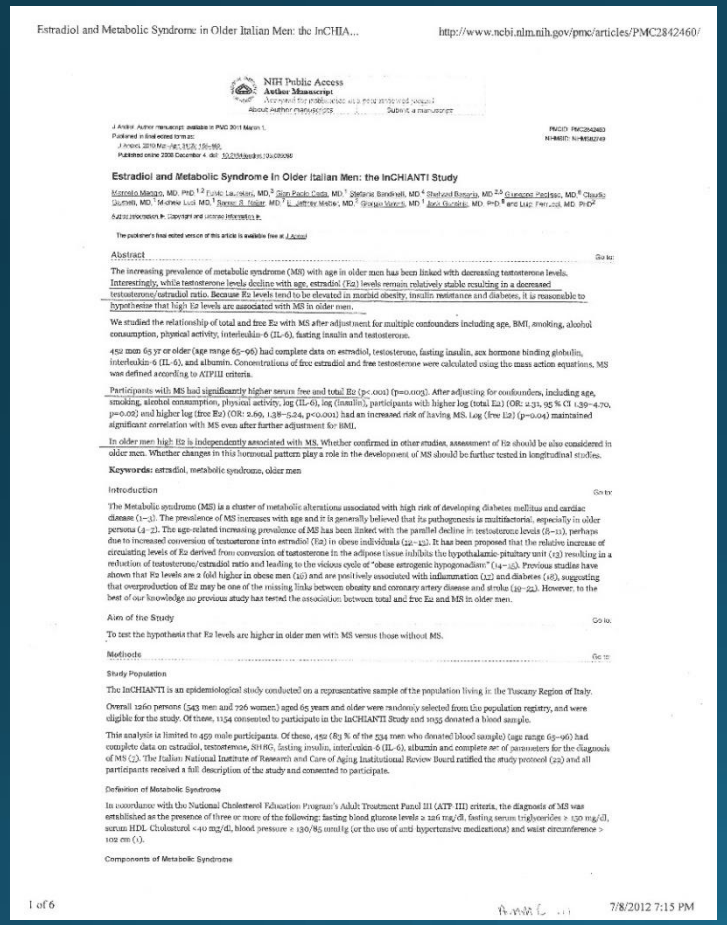
- Among men with chronic HF and reduced LVEF, high and low concentrations of estradiol compared with the middle quintile of estradiol are related to an increased mortality.

Jankowska EA, Rozentryt P, Ponikowska B, et al. Circulating estradiol and mortality in men with systolic chronic heart failure. *JAMA*. 2009 May 13;301(18):1892-901.

Estradiol and Metabolic Syndrome in Older Italian Men: the InCHIANTI Study



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Estradiol and Metabolic Syndrome in Older Italian Men: the InCHIANTI Study

Abstract

The increasing prevalence of metabolic syndrome (MS) with age in older men has been linked with decreasing testosterone levels. Interestingly, while testosterone levels decline with age, estradiol (E2) levels remain relatively stable resulting in a decreased testosterone/estradiol ratio. Because E2 levels tend to be elevated in morbid obesity, insulin resistance and diabetes, it is reasonable to hypothesize that high E2 levels are associated with MS in older men.

We studied the relationship of total and free E2 with MS after adjustment for multiple confounders including age, BMI, smoking, alcohol consumption, physical activity, interleukin-6 (IL-6), fasting insulin and testosterone.

452 men 65 yr or older (age range 65–96) had complete data on estradiol, testosterone, fasting insulin, sex hormone binding globulin, interleukin-6 (IL-6), and albumin. Concentrations of free estradiol and free testosterone were calculated using the mass action equations. MS was defined according to ATPIII criteria.

Participants with MS had significantly higher serum free and total E2 ($p<.001$) ($p=0.003$). After adjusting for confounders, including age, smoking, alcohol consumption, physical activity, log (IL-6), log (insulin), participants with higher log (total E2) (OR: 2.31, 95 % CI 1.39–4.70, $p=0.02$) and higher log (free E2) (OR: 2.69, 1.38–5.24, $p<0.001$) had an increased risk of having MS. Log (free E2) ($p=0.04$) maintained significant correlation with MS even after further adjustment for BMI.

In older men high E2 is independently associated with MS. Whether confirmed in other studies, assessment of E2 should be also considered in older men. Whether changes in this hormonal pattern play a role in the development of MS should be further tested in longitudinal studies.

Keywords: estradiol, metabolic syndrome, older men

Introduction

The Metabolic syndrome (MS) is a cluster of metabolic alterations associated with high risk of developing diabetes mellitus and cardiac disease (1–3). The prevalence of MS increases with age and it is generally believed that its pathogenesis is multifactorial, especially in older persons (4–7). The age-related increasing prevalence of MS has been linked with the parallel decline in testosterone levels (8–11), perhaps due to increased conversion of testosterone into estradiol (E2) in obese individuals (12–15). It has been proposed that the relative increase of circulating levels of E2 derived from conversion of testosterone in the adipose tissue inhibits the hypothalamic-pituitary unit (13) resulting in a reduction of testosterone/estradiol ratio and leading to the vicious cycle of "obese estrogenic hypogonadism" (14–15). Previous studies have shown that E2 levels are 2 fold higher in obese men (16) and are positively associated with inflammation (17) and diabetes (18), suggesting that overproduction of E2 may be one of the missing links between obesity and coronary artery disease and stroke (19–22). However, to the best of our knowledge no previous study has tested the association between total and free E2 and MS in older men.

Aim of the Study

To test the hypothesis that E2 levels are higher in older men with MS versus those without MS.

Methods

Study Population

The InCHIANTI is an epidemiological study conducted on a representative sample of the population living in the Tuscany Region of Italy.

Overall 1260 persons (543 men and 726 women) aged 65 years and older were randomly selected from the population registry, and were eligible for the study. Of these, 1154 consented to participate in the InCHIANTI Study and 1055 donated a blood sample.

This analysis is limited to 459 male participants. Of these, 452 (83 % of the 534 men who donated blood sample) (age range 65–96) had complete data on estradiol, testosterone, SHBG, fasting insulin, interleukin-6 (IL-6), albumin and complete set of parameters for the diagnosis of MS (3). The Italian National Institute of Research and Care of Aging Institutional Review Board ratified the study protocol (23) and all participants received a full description of the study and consented to participate.

Definition of Metabolic Syndrome

In accordance with the National Cholesterol Education Program's Adult Treatment Panel III (ATP III) criteria, the diagnosis of MS was established as the presence of three or more of the following: fasting blood glucose levels ≥ 126 mg/dl, fasting serum triglycerides ≥ 150 mg/dl, serum HDL Cholesterol <40 mg/dl, blood pressure ≥ 130/85 mmHg (or the use of anti hypertensive medications) and waist circumference > 102 cm (1).

Components of Metabolic Syndrome

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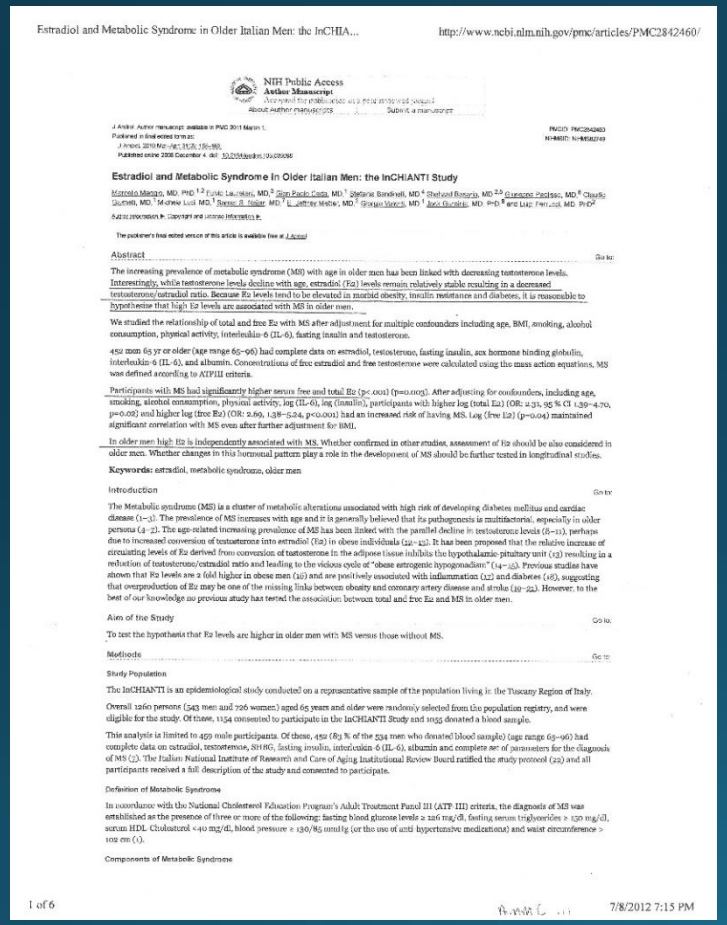
- Interestingly, while testosterone levels decline with age, estradiol (E2) levels remain relatively stable resulting in a decreased testosterone/estradiol ratio.
- Because E2 levels tend to be elevated in morbid obesity, insulin resistance and diabetes, it is reasonable to hypothesize that high E2 levels are associated with MS in older men.

Maggio M, Lauretani F, Ceda GP, et al. Estradiol and metabolic syndrome in older Italian men: The InCHIANTI Study. *J Androl*. 2010 Mar-Apr;31(2):155-62.

Estradiol and Metabolic Syndrome in Older Italian Men: the InCHIANTI Study



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Estradiol and Metabolic Syndrome in Older Italian Men: the InCHIANTI Study

Abstract

The increasing prevalence of metabolic syndrome (MS) with age in older men has been linked with decreasing testosterone levels. Interestingly, while testosterone levels decline with age, estradiol (E2) levels remain relatively stable resulting in a decreased testosterone/estradiol ratio. Because E2 levels tend to be elevated in morbid obesity, insulin resistance and diabetes, it is reasonable to hypothesize that high E2 levels are associated with MS in older men.

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Keywords: estradiol, metabolic syndrome, older men

Introduction

The Metabolic syndrome (MS) is a cluster of metabolic alterations associated with high risk of developing diabetes mellitus and cardiac disease (1–3). The prevalence of MS increases with age and it is generally believed that its pathogenesis is multifactorial, especially in older persons (4–7). The age-related increasing prevalence of MS has been linked with the parallel decline in testosterone levels (8–11), perhaps due to increased conversion of testosterone into estradiol (E2) in obese individuals (12–15). It has been proposed that the relative increase of circulating levels of E2 derived from conversion of testosterone in the adipose tissue inhibits the hypothalamic-pituitary unit (13) resulting in a reduction of testosterone/estradiol ratio and leading to the vicious cycle of "obese estrogenic hypogonadism" (14–16). Previous studies have shown that E2 levels are 2 fold higher in obese men (16) and are positively associated with inflammation (17) and diabetes (18), suggesting that overproduction of E2 may be one of the missing links between obesity and coronary artery disease and stroke (19–22). However, to the best of our knowledge no previous study has tested the association between total and free E2 and MS in older men.

Aim of the Study

To test the hypothesis that E2 levels are higher in older men with MS versus those without MS.

Methods

Study Population

The InCHIANTI is an epidemiological study conducted on a representative sample of the population living in the Tuscany Region of Italy.

Overall 1260 persons (543 men and 726 women) aged 65 years and older were randomly selected from the population registry, and were eligible for the study. Of these, 1154 consented to participate in the InCHIANTI Study and 1055 donated a blood sample.

This analysis is limited to 459 male participants. Of these, 452 (83 % of the 534 men who donated blood sample) (age range 65–96) had complete data on estradiol, testosterone, SHBG, fasting insulin, interleukin-6 (IL-6), albumin and complete set of parameters for the diagnosis of MS (3). The Italian National Institute of Research and Care of Aging Institutional Review Board ratified the study protocol (23) and all participants received a full description of the study and consented to participate.

Definition of Metabolic Syndrome

In accordance with the National Cholesterol Education Program's Adult Treatment Panel III (ATP III) criteria, the diagnosis of MS was established as the presence of three or more of the following: fasting blood glucose levels ≥ 126 mg/dl, fasting serum triglycerides ≥ 150 mg/dl, serum HDL Cholesterol <40 mg/dl, blood pressure ≥ 130/85 mmHg (or the use of anti hypertensive medications) and waist circumference > 102 cm (3).

Components of Metabolic Syndrome

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- Participants with MS had significantly high serum free and total E2.
- In older men high E2 is independently associated with MS.

Maggio M, Lauretani F, Ceda GP, et al. Estradiol and metabolic syndrome in older Italian men: The InCHIANTI Study. *J Androl*. 2010 Mar-Apr;31(2):155-62.

Hypogonadism as a risk factor for cardiovascular mortality in men: a meta-analytic study

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REVIEW

Hypogonadism as a risk factor for cardiovascular mortality in men: a meta-analytic study

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Abstract

Objective: To verify whether hypogonadism represents a risk factor for cardiovascular (CV) morbidity and mortality and to verify whether testosterone replacement therapy (TRT) improves CV parameters in subjects with known CV diseases (CVDs).

Design: Meta-analysis.

Methods: An extensive Medline search was performed using the following words 'testosterone, CVD, and males'. The search was restricted to data from January 1, 1969, up to January 1, 2011.

Results: Of the 1178 retrieved articles, 70 were included in the study. Among cross-sectional studies, patients with CVD have significantly lower testosterone and higher 17-β estradiol (E_2) levels. Conversely, no difference was observed for DHEAS. The association between low testosterone and high E_2 levels with CVD was confirmed in a logistic regression model, after adjusting for age and body mass index (hazard ratio (HR)=0.763 (0.744–0.783) and HR=1.015 (1.014–1.017), respectively, for each increment of total testosterone and E_2 levels; both $P<0.0001$). Longitudinal studies showed that baseline testosterone level was significantly lower among patients with incident overall- and CV-related mortality, in comparison with controls. Conversely, we did not observe any difference in the baseline testosterone and E_2 levels between case and controls for incident CVD. Finally, TRT was positively associated with a significant increase in treadmill test duration and time to 1 mm ST segment depression.

Conclusions: Lower testosterone (and higher E_2 levels) correlate with increased risk of CVD and CV mortality. TRT in hypogonadism moderates metabolic components associated with CV risk. Whether low testosterone is just an association with CV risk, or an actual cause–effect relationship, awaits further studies.

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Introduction

Cardiovascular disease (CVD) is the world's leading killer disease, and over 80% of deaths due to CVD occur in low- and middle-income countries (1). However, in all populations studied, CVD is more frequent and has a greater mortality risk in men than in women (2). In Europe, one in four men dies before the age of 75 years due to CVD, while the figure for women is only one in six. This gender-related difference is even more evident for deaths before the age of 65 years (12 vs 5% in men and women, respectively, see also www.heartstats.org/temp/ESspweb08spchapter.1.pdf). For coronary heart disease (CHD), women trail men in increased incidence by 10 years, although the gap closes with advancing age (3). The reasons for such gender difference have not been completely understood (4–10). However, sex hormones have been considered as a possible factor. Premenopausal women have been thought to have decreased risk of CVD because of their estrogen dominance, and it was presumed that men had an increased risk due to their androgens, although this has never been proven scientifically. The universal excess risk of CHD in men observed above, coupled with the apparent loss of the female advantage in women who had an early menopause and to the higher CV risk profile in women with hyperandrogenism, led to the hypothesis that the effects of endogenous estrogens and androgens are beneficial or harmful respectively. Data on the role of estrogens and DHEAS in the pathogenesis of male CVD are limited. Studies on the role of testosterone as a predictor of CV risk in men are

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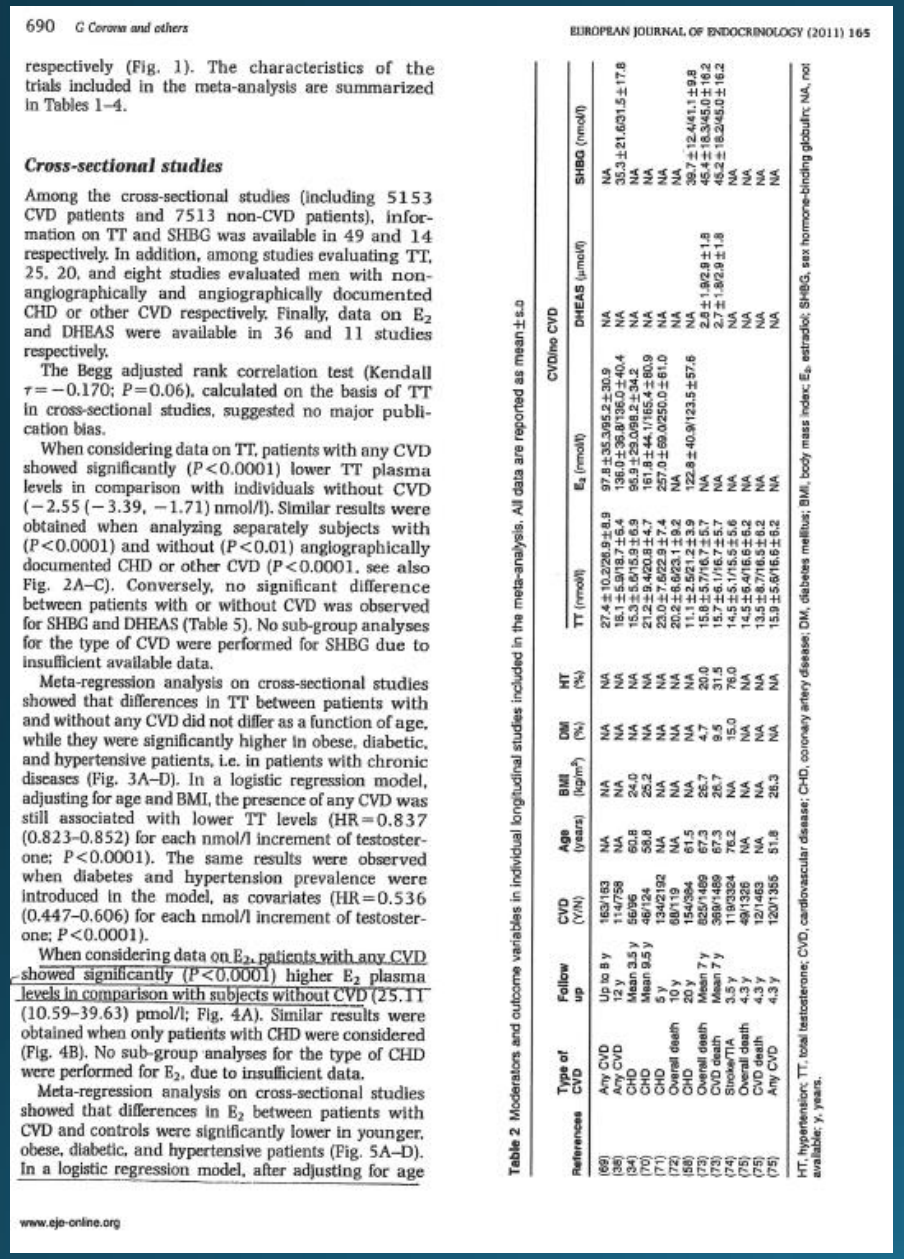
- *CONCLUSIONS:*
- Lower testosterone (and higher E2 levels) correlate with increased risk of CVD and CV mortality.
- TRT in hypogonadism moderates metabolic components associated with CV risk.
- Whether low testosterone is just an association with CV risk, or an actual cause-effect relationship, awaits further studies.

Corona, G., Rastrelli, G., Monami, M., Guay, A., Buvat, J., Sforza, A., . . . Maggi, M. (2011). Hypogonadism as a risk factor for cardiovascular mortality in men: a meta-analytic study. *European Journal of Endocrinology*.



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respectively (Fig. 1). The characteristics of the trials included in the meta-analysis are summarized in Tables 1–4.

Cross-sectional studies

Among the cross-sectional studies (including 5153 CVD patients and 7513 non-CVD patients), information on TT and SHBG was available in 49 and 14 respectively. In addition, among studies evaluating TT, 25, 20, and eight studies evaluated men with non-angiographically and angiographically documented CHD or other CVD respectively. Finally, data on E_2 and DHEAS were available in 36 and 11 studies respectively.

The Begg adjusted rank correlation test (Kendall $\tau = -0.170$; $P = 0.06$), calculated on the basis of TT in cross-sectional studies, suggested no major publication bias.

When considering data on TT, patients with any CVD showed significantly ($P < 0.0001$) lower TT plasma levels in comparison with individuals without CVD (−2.55 (−3.39, −1.71) nmol/l). Similar results were obtained when analyzing separately subjects with ($P < 0.0001$) and without ($P < 0.01$) angiographically documented CHD or other CVD ($P < 0.0001$, see also Fig. 2A–C). Conversely, no significant difference between patients with or without CVD was observed for SHBG and DHEAS (Table 5). No sub-group analyses for the type of CVD were performed for SHBG due to insufficient available data.

Meta-regression analysis on cross-sectional studies showed that differences in TT between patients with and without any CVD did not differ as a function of age, while they were significantly higher in obese, diabetic, and hypertensive patients, i.e. in patients with chronic diseases (Fig. 3A–D). In a logistic regression model, adjusting for age and BMI, the presence of any CVD was still associated with lower TT levels (HR = 0.837 (0.823–0.852) for each nmol/l increment of testosterone; $P < 0.0001$). The same results were observed when diabetes and hypertension prevalence were introduced in the model, as covariates (HR = 0.536 (0.447–0.606) for each nmol/l increment of testosterone; $P < 0.0001$).

When considering data on E_2, patients with any CVD showed significantly ($P < 0.0001$) higher E_2 plasma levels in comparison with subjects without CVD (25.11 (10.59–39.63) pmol/l; Fig. 4A). Similar results were obtained when only patients with CHD were considered (Fig. 4B). No sub-group analyses for the type of CHD were performed for E_2, due to insufficient data.

Meta-regression analysis on cross-sectional studies showed that differences in E_2 between patients with CVD and controls were significantly lower in younger, obese, diabetic, and hypertensive patients (Fig. 5A–D). In a logistic regression model, after adjusting for age

Table 2 Moderators and outcome variables in individual longitudinal studies included in the meta-analysis. All data are reported as mean ± s.d.

References	Type of CVD	Follow up	CVD (Y/N)	Age (years)	BMI (kg/m²)	DM (%)	HT (%)	CVD/no CVD			
								TT (nmol/l)	E_2 (nmol/l)	DHEAS (μmol/l)	SHBG (nmol/l)
(69)	Any CVD	Up to 8 y	163/183	NA	NA	NA	NA	27.4 ± 10.2/28.9 ± 8.9	97.8 ± 35.3/95.2 ± 30.9	NA	NA
(38)	Any CVD	12 y	114/758	NA	NA	NA	NA	18.1 ± 5.8/18.7 ± 5.4	136.0 ± 36.8/136.0 ± 40.4	NA	35.3 ± 21.6/31.5 ± 17.8
(34)	CHD	Mean 3.5 y	66/96	62.8	24.0	NA	NA	15.3 ± 5.6/15.9 ± 6.9	95.3 ± 29.0/98.2 ± 34.2	NA	NA
(70)	CHD	Mean 8.5 y	46/124	58.8	25.2	NA	NA	21.2 ± 9.4/20.8 ± 4.7	161.8 ± 44.1/165.4 ± 60.9	NA	NA
(71)	CHD	5 y	134/2192	NA	NA	NA	NA	23.0 ± 7.6/22.9 ± 7.4	257.0 ± 69.0/250.0 ± 61.0	NA	NA
(72)	Overall death	10 y	88/119	NA	NA	NA	NA	20.2 ± 6.6/23.1 ± 9.2	NA	NA	NA
(58)	CHD	20 y	154/384	61.5	NA	NA	NA	11.1 ± 2.5/21.2 ± 3.9	122.8 ± 40.9/123.5 ± 57.6	NA	39.7 ± 12.4/41.1 ± 9.8
(73)	Overall death	Mean 7 y	825/1469	67.3	26.7	4.7	20.0	15.8 ± 5.7/16.7 ± 5.7	NA	2.6 ± 1.9/2.9 ± 1.8	45.4 ± 16.3/45.0 ± 16.2
(74)	CVD death	Mean 7 y	369/1469	67.3	26.7	9.5	31.5	15.7 ± 6.1/16.7 ± 5.7	NA	2.7 ± 1.9/2.9 ± 1.8	45.2 ± 16.2/45.0 ± 16.2
(75)	Stroke/TIA	3.5 y	119/3324	76.2	NA	15.0	76.0	14.5 ± 5.1/15.5 ± 5.6	NA	NA	NA
(75)	Overall death	4.3 y	491/326	NA	NA	NA	NA	14.5 ± 6.4/16.6 ± 6.2	NA	NA	NA
(75)	CVD death	4.3 y	121/468	NA	NA	NA	NA	13.5 ± 8.7/16.5 ± 6.2	NA	NA	NA
(75)	Any CVD	4.3 y	120/1365	51.8	26.3	NA	NA	15.9 ± 5.6/16.6 ± 6.2	NA	NA	NA

HT, hypertension; TT, total testosterone; CVD, cardiovascular disease; CHD, coronary artery disease; DM, diabetes mellitus; BMI, body mass index; E_2, estradiol; SHBG, sex hormone-binding globulin; NA, not available; y, years.

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- When considering data on E2, patients with any CVD showed significantly ($p<0.0001$) higher E2 plasma levels in comparison with subjects without CVD.
- In a logistic regression model, after adjusting for age and BMI, the presence of any CVD was still associated with higher E2 levels.

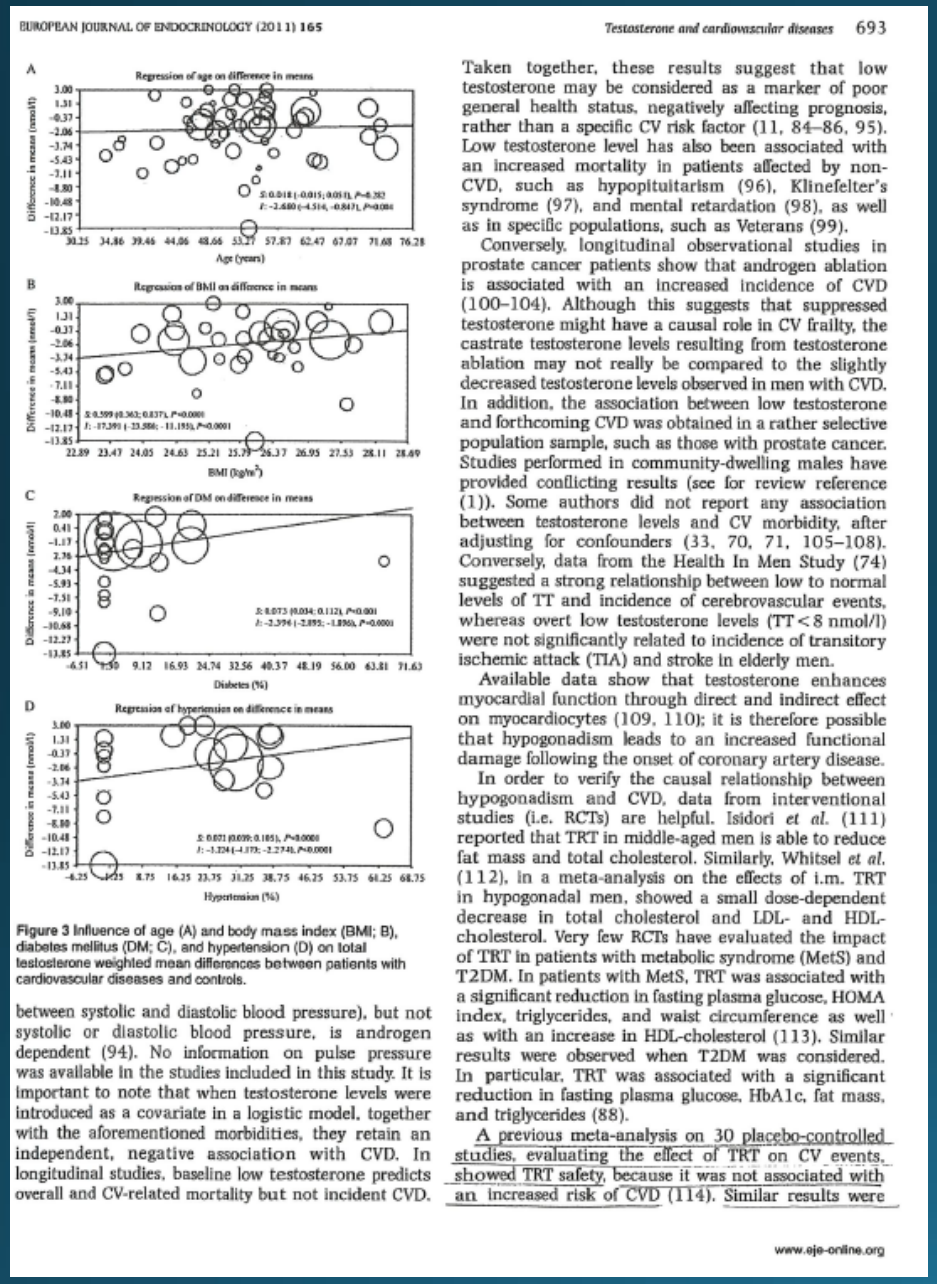

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Figure 3 Influence of age (A) and body mass index (BMI; B), diabetes mellitus (DM; C), and hypertension (D) on total testosterone weighted mean differences between patients with cardiovascular diseases and controls.

between systolic and diastolic blood pressure), but not systolic or diastolic blood pressure, is androgen dependent (94). No information on pulse pressure was available in the studies included in this study. It is important to note that when testosterone levels were introduced as a covariate in a logistic model, together with the aforementioned morbidities, they retain an independent, negative association with CVD. In longitudinal studies, baseline low testosterone predicts overall and CV-related mortality but not incident CVD. Taken together, these results suggest that low testosterone may be considered as a marker of poor general health status, negatively affecting prognosis, rather than a specific CV risk factor (11, 84–86, 95). Low testosterone level has also been associated with an increased mortality in patients affected by non-CVD, such as hypopituitarism (96), Klinefelter's syndrome (97), and mental retardation (98), as well as in specific populations, such as Veterans (99).

Conversely, longitudinal observational studies in prostate cancer patients show that androgen ablation is associated with an increased incidence of CVD (100–104). Although this suggests that suppressed testosterone might have a causal role in CV frailty, the castrate testosterone levels resulting from testosterone ablation may not really be compared to the slightly decreased testosterone levels observed in men with CVD. In addition, the association between low testosterone and forthcoming CVD was obtained in a rather selective population sample, such as those with prostate cancer. Studies performed in community-dwelling males have provided conflicting results (see for review reference (1)). Some authors did not report any association between testosterone levels and CV morbidity, after adjusting for confounders (33, 70, 71, 105–108). Conversely, data from the Health In Men Study (74) suggested a strong relationship between low to normal levels of TT and incidence of cerebrovascular events, whereas overt low testosterone levels (TT < 8 nmol/l) were not significantly related to incidence of transitory ischemic attack (TIA) and stroke in elderly men.

Available data show that testosterone enhances myocardial function through direct and indirect effect on myocardiocytes (109, 110); it is therefore possible that hypogonadism leads to an increased functional damage following the onset of coronary artery disease.

In order to verify the causal relationship between hypogonadism and CVD, data from interventional studies (i.e. RCTs) are helpful. Isidori *et al.* (111) reported that TRT in middle-aged men is able to reduce fat mass and total cholesterol. Similarly, Whitsel *et al.* (112), in a meta-analysis on the effects of i.m. TRT in hypogonadal men, showed a small dose-dependent decrease in total cholesterol and LDL- and HDL-cholesterol. Very few RCTs have evaluated the impact of TRT in patients with metabolic syndrome (MetS) and T2DM. In patients with MetS, TRT was associated with a significant reduction in fasting plasma glucose, HOMA index, triglycerides, and waist circumference as well as with an increase in HDL-cholesterol (113). Similar results were observed when T2DM was considered. In particular, TRT was associated with a significant reduction in fasting plasma glucose, HbA1c, fat mass, and triglycerides (88).

A previous meta-analysis on 30 placebo-controlled studies, evaluating the effect of TRT on CV events, showed TRT safety, because it was not associated with an increased risk of CVD (114). Similar results were

- A previous meta-analysis on 30 placebo-controlled studies, evaluating the effect of TRT on CV events, showed TRT safety, because it was not associated with an increased risk of CVD.
- Similar results were more recently reported by Fernandez-Balsells et al. who meta-analyzed 51 placebo-controlled studies with follow-up ranging from 3 months up to 3 years.

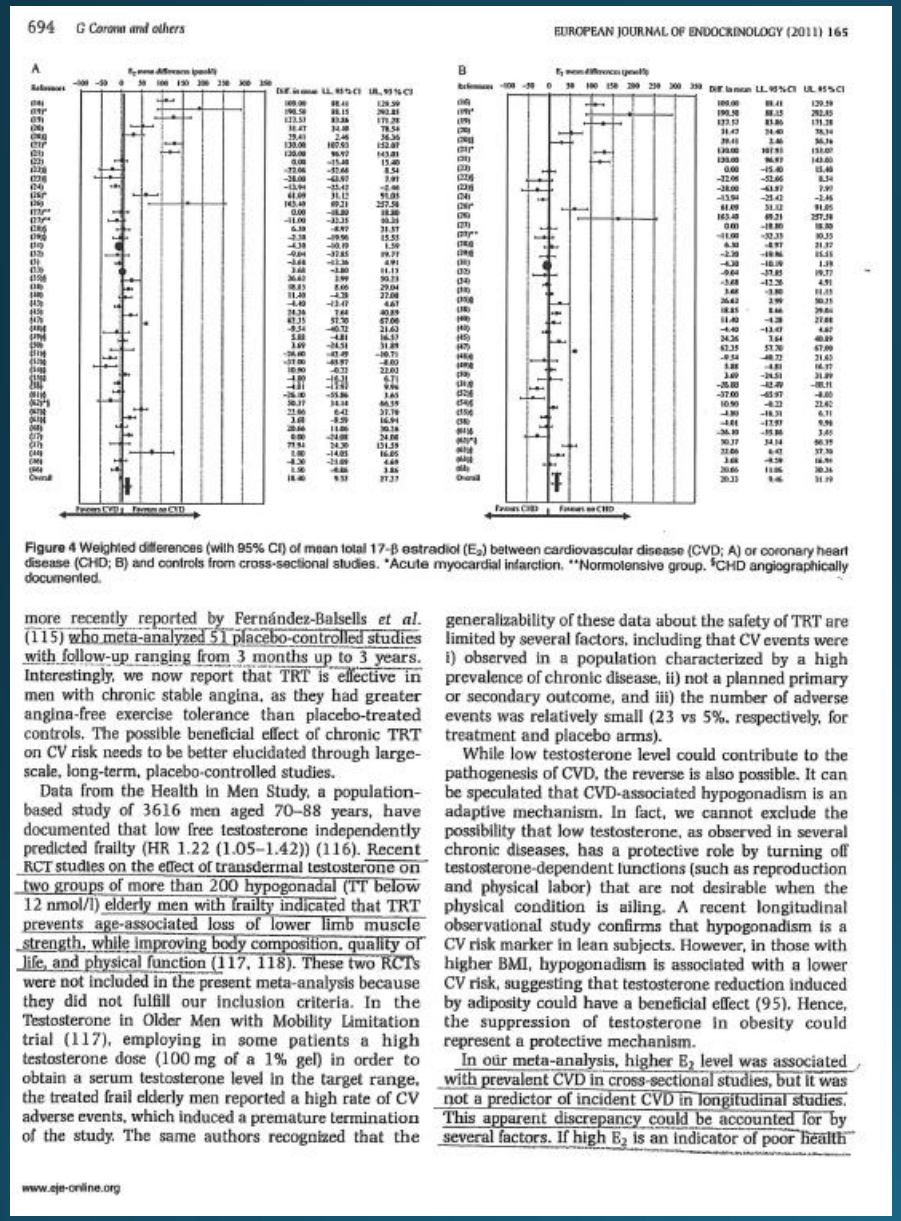

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Figure 4 Weighted differences (with 95% CI) of mean total 17-β estradiol (E_2) between cardiovascular disease (CVD; A) or coronary heart disease (CHD; B) and controls from cross-sectional studies. *Acute myocardial infarction. **Normotensive group. §CHD angiographically documented.

more recently reported by Fernández-Balsells *et al.* (115) who meta-analyzed 51 placebo-controlled studies with follow-up ranging from 3 months up to 3 years. Interestingly, we now report that TRT is effective in men with chronic stable angina, as they had greater angina-free exercise tolerance than placebo-treated controls. The possible beneficial effect of chronic TRT on CV risk needs to be better elucidated through large-scale, long-term, placebo-controlled studies.

Data from the Health in Men Study, a population-based study of 3616 men aged 70–88 years, have documented that low free testosterone independently predicted frailty (HR 1.22 (1.05–1.42)) (116). Recent RCT studies on the effect of transdermal testosterone on two groups of more than 200 hypogonadal (TT below 12 nmol/l) elderly men with frailty indicated that TRT prevents age-associated loss of lower limb muscle strength, while improving body composition, quality of life, and physical function (117, 118). These two RCTs were not included in the present meta-analysis because they did not fulfill our inclusion criteria. In the Testosterone in Older Men with Mobility Limitation trial (117), employing in some patients a high testosterone dose (100 mg of a 1% gel) in order to obtain a serum testosterone level in the target range, the treated frail elderly men reported a high rate of CV adverse events, which induced a premature termination of the study. The same authors recognized that the generalizability of these data about the safety of TRT are limited by several factors, including that CV events were i) observed in a population characterized by a high prevalence of chronic disease, ii) not a planned primary or secondary outcome, and iii) the number of adverse events was relatively small (23 vs 5%, respectively, for treatment and placebo arms).

While low testosterone level could contribute to the pathogenesis of CVD, the reverse is also possible. It can be speculated that CVD-associated hypogonadism is an adaptive mechanism. In fact, we cannot exclude the possibility that low testosterone, as observed in several chronic diseases, has a protective role by turning off testosterone-dependent functions (such as reproduction and physical labor) that are not desirable when the physical condition is ailing. A recent longitudinal observational study confirms that hypogonadism is a CV risk marker in lean subjects. However, in those with higher BMI, hypogonadism is associated with a lower CV risk, suggesting that testosterone reduction induced by adiposity could have a beneficial effect (95). Hence, the suppression of testosterone in obesity could represent a protective mechanism.

In our meta-analysis, higher E_2 level was associated with prevalent CVD in cross-sectional studies, but it was not a predictor of incident CVD in longitudinal studies. This apparent discrepancy could be accounted for by several factors. If high E_2 is an indicator of poor health

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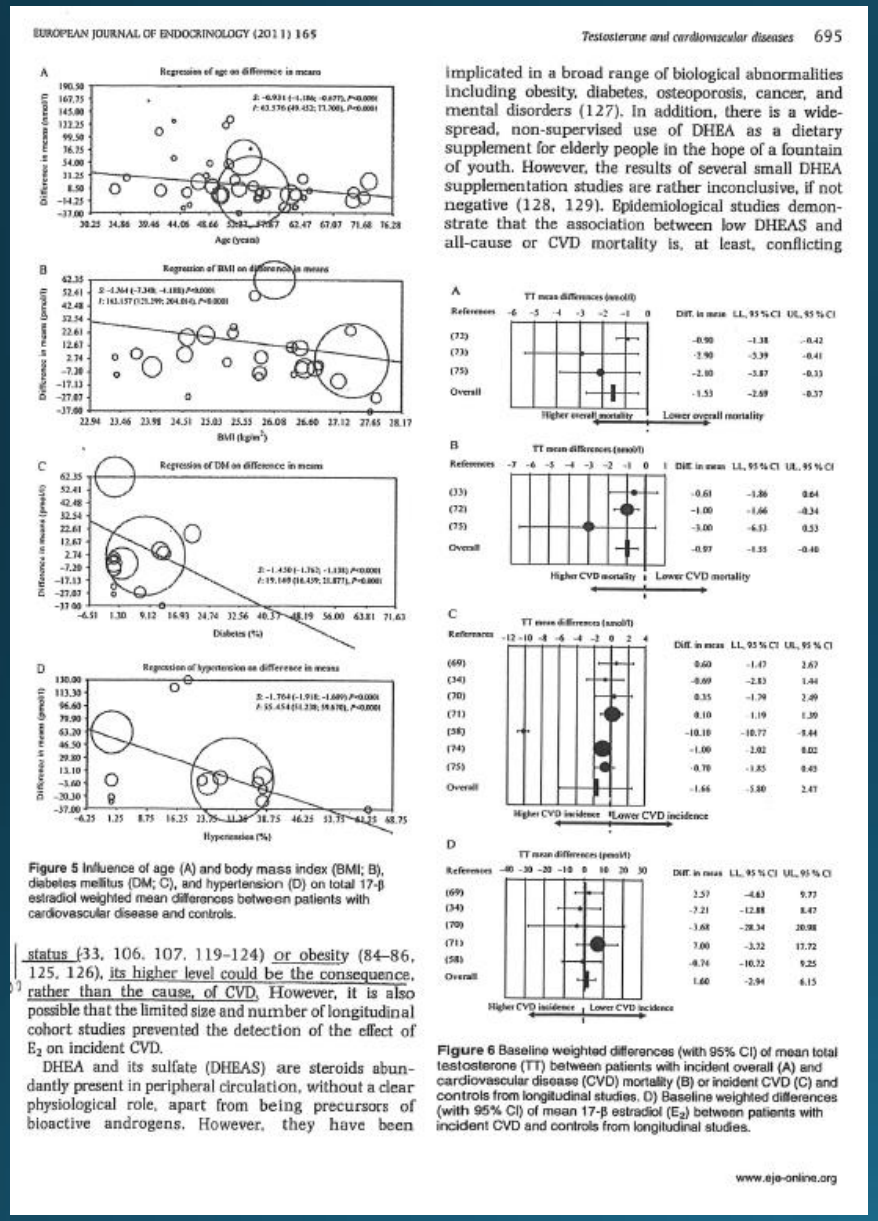

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Figure 5 Influence of age (A) and body mass index (BMI; B), diabetes mellitus (DM; C), and hypertension (D) on total 17-β estradiol weighted mean differences between patients with cardiovascular disease and controls.

status (33, 106, 107, 119–124) or obesity (84–86, 125, 126), its higher level could be the consequence, rather than the cause, of CVD. However, it is also possible that the limited size and number of longitudinal cohort studies prevented the detection of the effect of E_2 on incident CVD.

DHEA and its sulfate (DHEAS) are steroids abundantly present in peripheral circulation, without a clear physiological role, apart from being precursors of bioactive androgens. However, they have been implicated in a broad range of biological abnormalities including obesity, diabetes, osteoporosis, cancer, and mental disorders (127). In addition, there is a widespread, non-supervised use of DHEA as a dietary supplement for elderly people in the hope of a fountain of youth. However, the results of several small DHEA supplementation studies are rather inconclusive, if not negative (128, 129). Epidemiological studies demonstrate that the association between low DHEAS and all-cause or CVD mortality is, at least, conflicting

Figure 6 Baseline weighted differences (with 95% CI) of mean total testosterone (TT) between patients with incident overall (A) and cardiovascular disease (CVD) mortality (B) or incident CVD (C) and controls from longitudinal studies. D) Baseline weighted differences (with 95% CI) of mean 17-β estradiol (E_2) between patients with incident CVD and controls from longitudinal studies.

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- If high E2 is an indicator of poor health status or obesity, its higher level could be the consequence rather than the cause of CVD.

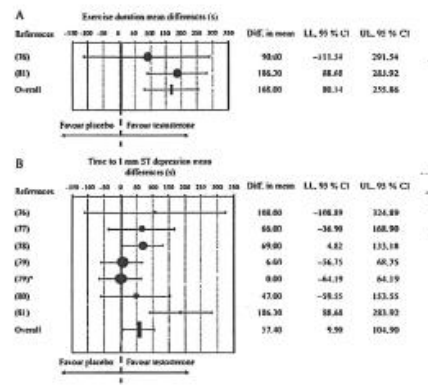

Figure 7 Weighted differences (with 95% CI) of mean treadmill test duration (A) and time to 1 mm ST segment depression (B) during treadmill test at endpoint across randomized controlled trials. *Supra-physiologic (6× baseline) serum testosterone level.

(130–135). Our study found no significant relationship between DHEAS levels and CVD.

Several limitations should be recognized. Potential selection bias and confounding factors may exist. Several longitudinal studies evaluating the incidence of CVD or CVD mortality were not included in the present meta-analysis, since they do not report continuous hormone values. Data on E_2 should be considered with caution since the assays used in these publications is missing. The number and the duration of RCTs as well as the number of the patients enrolled are very limited. However, it should be important to emphasize that we considered only studies evaluating the effect of TRT on CV parameters derived from treadmill test in men with chronic stable angina. Further prospective investigations on TRT in CVD and CHD patients are advisable.

Conclusions

This meta-analysis of the relationship between testosterone and CVD, risks and consequences, reinforces many other studies but unifies several of the concepts previously published separately. Low testosterone levels have been shown to correlate significantly with CV risk factors but also with the incidence of CHD events, and indeed, with the incidence of CVD events in general. This also correlates with the ultimate risk of mortality itself. This is very important as the review began by reminding us that death due to CVD is the most common cause of mortality in men. One interesting finding was that the increase in CVD was associated with medical co-factors, especially obesity, diabetes, and hypertension, and not a function of age *per se*. These findings were also accompanied by a higher E_2 level, which may be more a result of the medical conditions and risks, rather than a cause. It is therefore very important that clinicians look for hypogonadism in men with CV risk factors and disease and conversely look for CV comorbidities when hypogonadism is found. The encouraging news is that early studies have shown that treatment of low testosterone states may moderate many of the medical co-factors and thus may decrease CV risks (136). This has to be proven with much larger numbers followed over a longer period of time so that we can see whether treatment of hypogonadism may actually decrease CV events, data that we do not have at this point in time. This conclusion leads to an unsolved dilemma: is low testosterone level in CVD a positive consequence of the body trying to decrease unnecessary energy by reducing reproductive expenditure in order to survive, or does it represent a pathophysiologic factor in the same illness? In the first scenario, testosterone supplementation may not be advisable, whereas in the second scenario it would be recommended. Present available data are not sufficient to sort out the beneficial or harmful effects of TRT on CV morbidity and mortality.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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- These findings of obesity and DM were also accompanied by a higher E2 level, which may be more a result of the medical conditions and risks, rather than a cause.
- The encouraging news is that early studies have shown that treatment of low testosterone states may moderate many of the medical co-factors and thus may decrease CV risks.

Endogenous oestradiol and cardiovascular disease in healthy men: a systematic review and meta-analysis of prospective studies.

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Systematic review

Endogenous oestradiol and cardiovascular disease in healthy men: a systematic review and meta-analysis of prospective studies

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Contributors GV, PC: Drafting, collection, analysis, interpretation of data. TF, JMK: Interpretation of data and revision of manuscript. DDB, DMO, JBR: Design, analysis, interpretation of data and revision of manuscript.

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Abstract

Context The literature provides no clear answer as to whether total oestradiol (E2) concentrations increase the risk of incident cardiovascular disease (CVD) in healthy men.

Objective The authors conducted a systematic review and meta-analysis to estimate the predictive value of E2 for CVD, and to identify study features explaining conflicting results.

Data sources Articles were identified by a Medline and Embase search and citation tracking.

Study selection Eligible articles were prospective population-based cohorts and nested case-control studies on E2 and incident cardiovascular disease (CVD), including myocardial infarction, stroke or death from coronary heart disease.

Data extraction Independent researchers re-expressed associations of E2 and incident CVD in a uniform manner to be used in meta-regression analyses for identification of study features explaining conflicting results, and to estimate the predictive value of E2 for CVD.

Results and conclusions 14 studies out of 128 electronically identified articles were eligible. Data to be used for meta-analysis could be calculated in seven cases, and in the remaining seven cases, data of three more became available by contacting those authors. Overall, a non-significant association was found with an estimated summary RR of 0.98 for a change of >75th versus <25th percentile in E2 (95% CI 0.74 to 1.31). Mean body mass index (BMI) of the study population (βs −0.8, p<0.004), and quality of E2 assay (βs −0.6, p<0.08) may have modified the relationship between E2 and incident CVD. The present systematic review does not provide evidence for a pronounced harmful or beneficial effect of E2 on risk for incident CVD in healthy men. If present, an effect of E2 on risk for CVD might be modulated by BMI.

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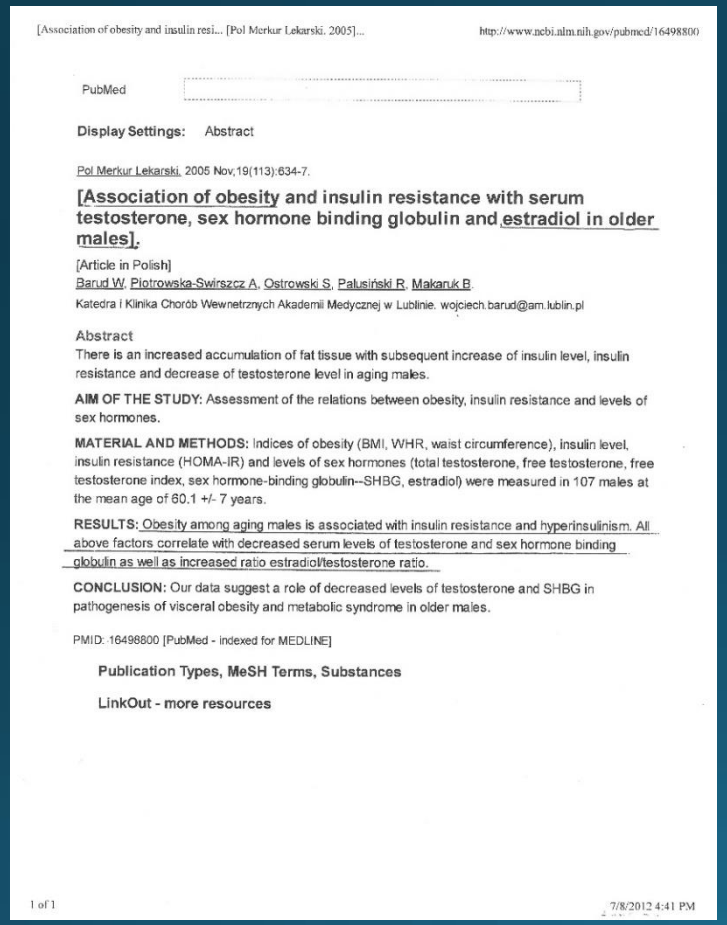
- Mean body mass index (BMI) of the study population may have modified the relationship between E2 and incident CVD.
- If present an effect of E2 on risk for CVD might be modulated by BMI.

Vandenplas G, De Bacquer D, Calders P, et al. Endogenous oestradiol and cardiovascular disease in healthy men: a systematic review and meta-analysis of prospective studies. Heart. 2012 Oct;98(20):1478-82.

Association of obesity and insulin resistance with serum testosterone, sex hormone binding globulin and estradiol in older males.



[Association of obesity and insulin resi... [Pol Merkur Lekarski. 2005]... http://www.ncbi.nlm.nih.gov/pubmed/16498800

PubMed

Display Settings: Abstract

Pol Merkur Lekarski. 2005 Nov;19(113):634-7.

[Association of obesity and insulin resistance with serum testosterone, sex hormone binding globulin and estradiol in older males].

[Article in Polish]

Barud W, Piotrowska-Swirszcz A, Ostrowski S, Palusiński R, Makaruk B.

Katedra i Klinika Chorób Wewnetrznych Akademii Medycznej w Lublinie. wojciech.barud@am.lublin.pl

Abstract

There is an increased accumulation of fat tissue with subsequent increase of insulin level, insulin resistance and decrease of testosterone level in aging males.

AIM OF THE STUDY: Assessment of the relations between obesity, insulin resistance and levels of sex hormones.

MATERIAL AND METHODS: Indices of obesity (BMI, WHR, waist circumference), insulin level, insulin resistance (HOMA-IR) and levels of sex hormones (total testosterone, free testosterone, free testosterone index, sex hormone-binding globulin--SHBG, estradiol) were measured in 107 males at the mean age of 60.1 +/- 7 years.

RESULTS: Obesity among aging males is associated with insulin resistance and hyperinsulinism. All above factors correlate with decreased serum levels of testosterone and sex hormone binding globulin as well as increased ratio estradiol/testosterone ratio.

CONCLUSION: Our data suggest a role of decreased levels of testosterone and SHBG in pathogenesis of visceral obesity and metabolic syndrome in older males.

PMID: 16498800 [PubMed - indexed for MEDLINE]

Publication Types, MeSH Terms, Substances

LinkOut - more resources

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- Obesity among aging males is associated with insulin resistance and hyperinsulinism.
- All above factors correlate with decreased serum levels of testosterone and sex hormone binding globulin as well as increased estrogen.

Barud W, Piotrowska-Swirszcz A, Ostrowski S, et al. Association of obesity and insulin resistance with serum testosterone, sex hormone binding globulin and estradiol in older males. *Pol Merkur Lekarski.* 2005 Nov;19(113):634-7.

Endogenous Sex Hormones and Cardiovascular Disease Incidence in Men

Annals of Internal Medicine | ARTICLE

Endogenous Sex Hormones and Cardiovascular Disease Incidence in Men

Johan Ärnlöv, MD, PhD; Michael J. Pencina, PhD; Shreyasee Amin, MD; Byung-Ho Nam, PhD; Emelia J. Benjamin, MD, ScM; Joanne M. Murabito, MD, ScM; Thomas J. Wang, MD; Philip E. Knapp, MD; Ralph B. D'Agostino Sr., PhD; Shalendar Bhasin, MD; and Ramachandran S. Vasan, MD

Background: Data suggest that endogenous sex hormones (testosterone, dehydroepiandrosterone sulfate [DHEA-S], and estradiol) influence cardiovascular disease (CVD) risk factors and vascular function. Yet, prospective studies relating sex hormones to CVD incidence in men have yielded inconsistent results.

Objective: To examine the association of circulating sex hormone levels and CVD risk in men.

Design: Prospective cohort study.

Setting: Community-based study in Framingham, Massachusetts.

Participants: 2084 middle-aged white men without CVD at baseline.

Measurements: The authors used multivariable Cox regression to relate baseline levels of testosterone, DHEA-S, and estradiol to the incidence of CVD (coronary, cerebrovascular, or peripheral vascular disease or heart failure) during 10 years of follow-up.

Results: During follow-up, 386 men (18.5%) experienced a first CVD event. After adjustment for baseline standard CVD risk factors, higher estradiol level was associated with lower risk for CVD (hazard ratio per SD increment in log estradiol, 0.90 [95% CI, 0.82 to 0.99]; $P = 0.035$). The authors observed effect modification by age: Higher estradiol levels were associated with lower CVD risk in older (median age >66 years) men (hazard ratio per SD increment, 0.86 [CI, 0.78 to 0.96]; $P = 0.005$) but not in younger (median age ≤66 years) men (hazard ratio per SD increment, 1.11 [CI, 0.89 to 1.38]; $P = 0.36$). The association of higher estradiol level with lower CVD incidence remained robust in time-dependent Cox models (updating standard CVD risk factors during follow-up). Serum testosterone and DHEA-S levels were not statistically significantly associated with incident CVD.

Limitations: Sex hormone levels were measured only at baseline, and the findings may not be generalizable to women and nonwhite people.

Conclusions: In the community-based sample, a higher serum estradiol level was associated with lower risk for CVD events in older men. The findings are consistent with the hypothesis that endogenous estrogen has vasculoprotective influences in men.

Ann Intern Med. 2006;145:176-184. www.annals.org

For author affiliation, see end of text.

Male sex is an independent risk factor for cardiovascular disease (CVD) (1). Scientists have postulated that the 5- to 10-year lag period in CVD incidence in women (compared with men) may be related to differences in endogenous sex hormones (2–7). Indeed, substantial evidence suggests that sex hormones (testosterone, estrogen, and dehydroepiandrosterone sulfate [DHEA-S]) influence traditional and newer CVD risk factors (2–7). Interest in the role of sex hormones in the pathogenesis of CVD has been rekindled by the observation that men with genetic defects of estrogen synthesis (8) or action (9) develop premature atherosclerosis. In addition, genetic variation in estrogen receptor-α has been associated with prevalent CVD (10, 11), and androgen and estrogen receptor expression in coronary arteries has been reported to influence coronary atherosclerosis in men (12).

In contrast to the aforementioned data, prospective studies relating circulating sex hormone levels to incident CVD in men have been inconclusive. For example, low serum testosterone levels have been associated with greater progression of subclinical atherosclerosis in 2 previous investigations (13, 14), but other studies have reported no association of testosterone levels with CVD events (15–21). On a parallel note, low DHEA-S levels have been linked to greater CVD risk in some studies (18, 22–24) but not in other studies (13, 20, 25–29). Investigations relating serum estradiol levels to CVD risk in men have generally found no statistically significant association (15–20). Some previous investigations were limited by modest sample sizes (14, 17, 18, 22, 25, 26); an insufficient number of CVD events (15–18, 22, 23, 26); and, in some instances, a retrospective study design (17–21, 25, 26). In addition, some reports (15, 22, 24) focused on CVD death (they did not evaluate nonfatal CVD events). Thus, a large prospective community-based study relating sex hormones to CVD risk with adequate power to detect modest potential associations is needed. Accordingly, we evaluated the associations of serum levels of sex hormones that were measured at a routine baseline examination with CVD incidence in a prospectively assembled cohort of participants.

See also:

Print
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Web-Only
Appendix Table
Conversion of figure and tables into slides

- A higher serum estradiol level was associated with lower risk for CVD events (in normal men).
- The findings are consistent with the hypothesis that endogenous estrogen has vasculoprotective influences in men.

Arnlöv J, Pencina MJ, Amin S, et al. Endogenous sex hormones and cardiovascular disease incidence in men. *Ann Intern Med*. 2006 Aug 1;145(3):176-84.

Endogenous Sex Hormones and Cardiovascular Disease in Men

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CARDIOVASCULAR ENDOCRINOLOGY

Endogenous Sex Hormones and Cardiovascular Disease in Men

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Unlike women, men do not experience an abrupt reduction in endogenous sex hormone production. It has, however, become clear that an age-associated decrease in the levels of (bioactive) sex hormones does occur. Whether endogenous sex hormones have an impact on cardiovascular disease has for many years remained largely unknown, but during the last decade more attention has been drawn to the importance of testosterone, estrogens, and adrenal androgens in etiology, prevention, and treatment of male cardiovascular disease. The purpose of this article is to summarize the evidence currently available on the association between endogenous sex hormones and cardiovascular disease in males. Published studies dealing with the relationship between circulating levels of sex hormones and cardiovascular disease in males were reviewed. The studies reviewed in this article suggest that circulating endogenous sex hormones and estrogens have a neutral or beneficial effect on cardiovascular disease in men. (*J Clin Endocrinol Metab* 88: 5076–5086, 2003)

ABUSE OF EXTREMELY high doses of anabolic steroids has been linked to sudden cardiac death, leading many to believe that the physiologically high levels of androgens in men may have a deleterious effect on the male cardiovascular system (1). However, recent reports contradict this theory, claiming that androgens may have cardiovascular benefits in men (2, 3).

The age-related decline in sex hormones in men (4) is hypothesized to promote age-related health problems. For many years, little was known about sex hormones and cardiovascular disease (CVD), but in the last decade the importance of testosterone (T) and dehydroepiandrosterone (DHEA), including its sulfate (DHEA-S), in CVD in men had been recognized.

This review summarizes current evidence on the association between sex hormones, endogenous as well as exogenous, and intermediate or clinically manifest indications of CVD and conditions in men.

Search strategy and selection criteria

Data for this review were identified by searches of MEDLINE and PubMed with the search terms "androgens" or "sex hormones" in combination with the terms "cardiovascular" and "males" or "men." We then searched these publications using the terms "diabetes," "cholesterol," "obesity," "atherosclerosis," "hypertension," and "vascular function." We focused on publications in the past decade but did not exclude commonly referenced and highly regarded older publications. Relevant articles not identified with the search strategy described above but referenced in the bibliographies of these papers could also be included. Several recent review articles and book chapters were also included because they provide comprehensive overviews.

Sex hormone biosynthesis and metabolism

Circulating steroids of importance in men are T, dihydrotestosterone, and estradiol. T is mainly produced by the testicles, whereas DHEA and DHEA-S are mainly produced by the adrenal glands. Both organs produce androstenedione (5). Figure 1 presents the several pathways for androgen and estrogen biosynthesis.

Androgens and estrogens circulate either free (1–2% of T) or bound to the serum proteins, albumin (binds 40–60% of T) and SHBG (binds 40–80% of T, which is biologically inactive) (6). Bioactive (bioavailable) T (BT) includes both free and albumin-bound T. Androstenedione and DHEA circulate weakly bound to albumin. DHEA-S binds strongly to albumin.

Measuring hormone levels

Reported concentrations of sex hormones vary widely, which may in part be due to the choice of laboratory assays used (7). Although indirect methods have been the gold standard, direct assays can provide accurate relative results except for low concentrations (6) (Table 1).

There is no real consensus as to which forms of hormones should be measured to best evaluate androgen status, and there is a need to standardize the procedures used to measure

Abbreviations: BT, Bioactive (bioavailable) T; CHD, coronary heart disease; CI, confidence interval; CVD, cardiovascular disease; DHEA, dehydroepiandrosterone; DHEA-S, DHEA sulfate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; Lpa, lipoprotein(a); MI, myocardial infarction; NO, nitric oxide; OR, odds ratio; PWV, pulse wave velocity; T, testosterone; tHcy, homocysteine.

- The studies reviewed in this article suggest that circulating endogenous sex hormones and estrogens have a neutral or beneficial effect on cardiovascular disease in men.

Muller M, van der Schouw YT, Thijssen JH, Grobbee DE. Endogenous sex hormones and cardiovascular disease in men. *J Clin Endocrinol Metab*. 2003 Nov;88(11):5076-86.

So there are 2 ways of blocking estrogen in men:

- ADT with LHRH inhibitors
- Aromatase inhibitors

- And so what happens when we block estrogen in men?

Effects of transdermal estrogen on levels of lipids, lipase activity, and inflammatory markers in men with prostate cancer

Effects of transdermal estrogen on levels of lipids, lipase activity, and... http://www.jlr.org/content/47/2/349.abstract

Journal of Lipid Research
www.jlr.org

First Published on November 20, 2005, doi: 10.1194/jlr.M500276-JLR200
February 2006 The Journal of Lipid Research, 47, 349-355.

Effects of transdermal estrogen on levels of lipids, lipase activity, and inflammatory markers in men with prostate cancer

Jonathan Q. Purnell[1,*,†], Lisa B. Bland[§], Mark Garzotto[§], Dianne Lemmon[**], Emily M. Wersinger[**], Christopher W. Ryan[**], John D. Brunzell[††] and Tomasz M. Beer[**]

Author Affiliations

[1]To whom correspondence should be addressed. e-mail: purnellj@ohsu.edu

ABSTRACT

Androgen deprivation therapy (ADT) for prostate cancer is now used in earlier disease stages and as adjuvant treatment. Recognizing and reducing the toxicity of this therapy, including worsened lipid levels and cardiovascular disease (CVD) risks, has become an important clinical concern. Oral estrogen therapy induces hypogonadism and mitigates many side effects of ADT, but has a high thrombosis risk. Transdermal estrogen therapy (TDE) has a lower thrombosis risk than oral estrogen and may improve CVD risk compared with ADT. This prospective pilot study of 18 men with androgen-independent prostate cancer receiving ADT measured effects of TDE on lipid and inflammatory CVD risk factors before and after 8 weeks of TDE (estradiol 0.6 mg/day). During treatment, estradiol levels rose 17-fold; total cholesterol, LDL cholesterol, and apolipoprotein B levels decreased. HDL_2 cholesterol increased, with no changes in triglyceride or VLDL cholesterol levels. Dense LDL cholesterol decreased and LDL buoyancy increased in association with a decrease in HL activity. Highly sensitive C-reactive protein levels and other inflammatory markers did not worsen. Compared with ADT, short-term TDE therapy of prostate cancer improves lipid levels without deterioration of CVD-associated inflammatory markers and may, on longer-term follow-up, improve CVD and mortality rates.

estradiol apolipoprotein inflammation androgen deprivation therapy

FOOTNOTES

Published, JLR Papers in Press, November 20, 2005.

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Purnell JQ, Bland LB, Garzotto M, et al. Effects of transdermal estrogen on levels of lipids, lipase activity, and inflammatory markers in men with prostate cancer. *J Lipid Res*. 2006 Feb;47(2):349-55.

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estradiol apolipoprotein inflammation androgen deprivation therapy

FOOTNOTES

Published JLR Papers in Press, November 20, 2005.

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- 8 weeks of TDE 0.6 mg/day resulted in:
- Total cholesterol, LDL cholesterol, and apolipoprotein B levels decreased.
- HDL_2 cholesterol increased.
- TDE on longer-term follow-up, improves lipids, CVD and mortality rates.

Purnell JQ, Bland LB, Garzotto M, et al. Effects of transdermal estrogen on levels of lipids, lipase activity, and inflammatory markers in men with prostate cancer. *J Lipid Res*. 2006 Feb;47(2):349-55.

Low-Dose Estrogen Supplementation Improves Vascular Function in Hypogonadal Men

Low-Dose Estrogen Supplementation Improves Vascular Function in... http://hyper.ahajournals.org/content/38/5/1011.abstract

Hypertension
hyper.ahajournals.org

Hypertension. 2001;38:1011-1016
doi: 10.1161/hy1101.095006

Scientific Contributions

Low-Dose Estrogen Supplementation Improves Vascular Function in Hypogonadal Men

Paul A. Komesaroff, Meryl Fullerton, Murray D. Esler, Anthony Dart, Garry Jennings, Krishnankutty Sudhir

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Correspondence to Dr K. Sudhir, Alfred Heart Center, 3rd Floor, Alfred Hospital, Commercial Rd, Prahran, VIC 3181, Australia. E-mail k.sudhir@alfred.org.au

Abstract

It is widely accepted that in women, estrogens provide protection against the development of cardiovascular disease. However, the cardiovascular role of estrogens in men remains uncertain, despite preliminary evidence that endogenous estrogens produced by aromatization of androgenic precursors are of physiological importance. Hypogonadal men have very low levels of circulating estrogen. We studied the responsiveness of forearm resistance arteries to vasoconstrictor and vasodilator agents in 12 men (mean±SEM age, 68.7±2.6 years) rendered hypogonadal as a result of treatment for prostatic cancer, before and after 8 weeks of estrogen supplementation (estradiol valerate 1 mg daily; n=7) or placebo (n=5). Forearm blood flow was measured by venous occlusion plethysmography, and vasoactive agents were infused through a brachial artery cannula in doses that did not affect blood pressure or heart rate. Estrogen supplementation was well tolerated, with no adverse effects. After estrogen treatment, mean estradiol levels increased from <30 to 308±65 pmol/L, and both systolic and diastolic blood pressures were reduced. HDL cholesterol levels increased significantly, and vasoconstrictor responses to the NO synthase inhibitor N^G-monomethyl-L-arginine (1, 2, 4 μmol/min) were enhanced. Vasoconstrictor responses to angiotensin II (8, 16, 32 ng/min) were markedly attenuated by estrogen treatment, as were vasoconstrictor responses to norepinephrine (25, 50, 100 ng/min). Estrogen did not alter the vasodilator responses to acetylcholine (9.25, 18.5, 37 μg/min) or to the endothelium-independent agent sodium nitroprusside (1.6 μg/min). Responses to all vasoactive agents were unchanged after administration of placebo. We conclude that low-dose estrogen supplementation in hypogonadal men is well tolerated, lowers blood pressure, and may affect vascular reactivity in a manner that is potentially beneficial, through several mechanisms, including enhancement of basal NO release and attenuation of vasoconstrictor responses to angiotensin II and norepinephrine. These findings suggest the need to consider a possible clinical role for estrogenic compounds in cardiovascular risk reduction in some groups of men.

Key Words:
estrogen
men

1 of 3 7/10/2012 7:58 PM

Komesaroff PA, Fullerton M, Esler MD, et al. Low-dose estrogen supplementation improves vascular function in hypogonadal men. *Hypertension*. 2001 Nov;38(5):1011-6.

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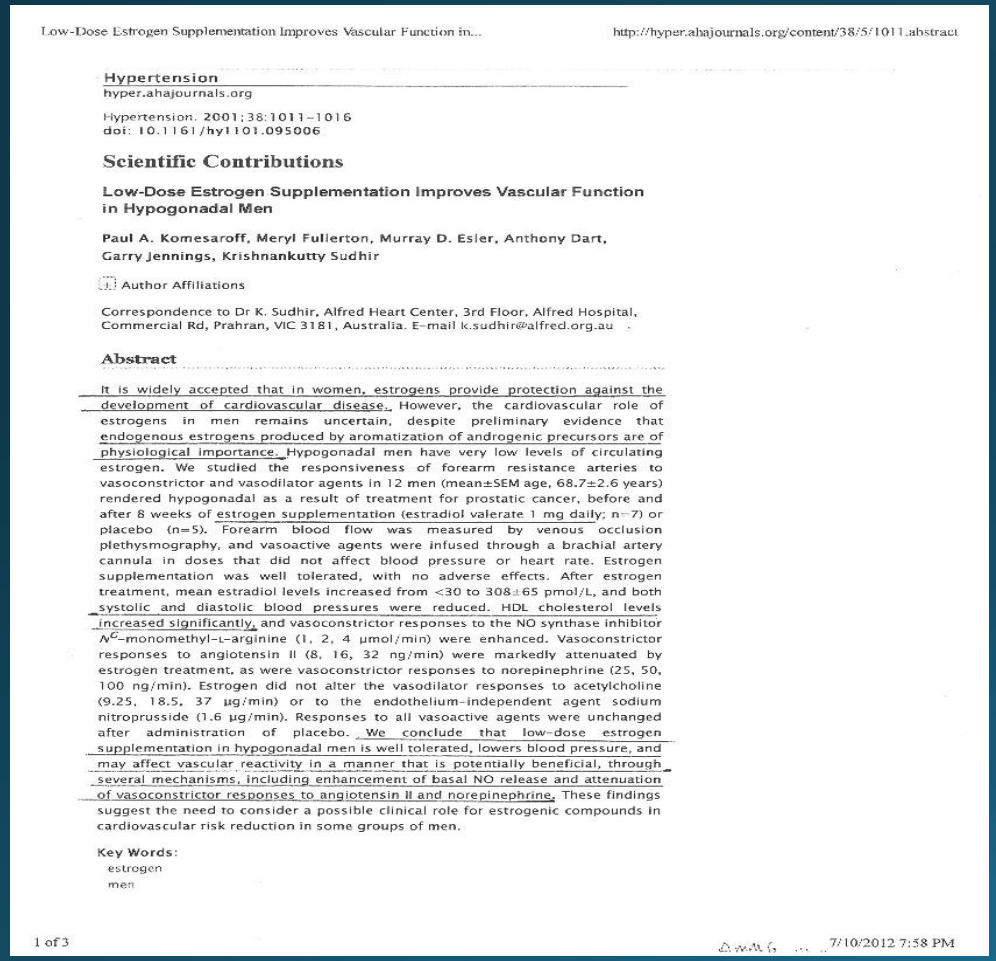
- Estrogen supplementation (estradiol 1 mg daily) was studied.

Low-Dose Estrogen Supplementation Improves Vascular Function in Hypogonadal Men



Hypertension
hyper.ahajournals.org

Hypertension. 2001;38:1011-1016
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Scientific Contributions

Low-Dose Estrogen Supplementation Improves Vascular Function in Hypogonadal Men

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Role of Estrogens in the Regulation of Membrane Microviscosity

Role of Estrogens in the Regulation of Membrane Microviscosity http://circres.ahajournals.org/content/94/2/e17.full

Circulation Research
circres.ahajournals.org

Circulation Research. 2004;94:e17
doi: 10.1161/01.RES.0000115311.56442.A6

Letters to the Editor

Role of Estrogens in the Regulation of Membrane Microviscosity

Kazushi Tsuda, Ichiro Nishio

Author Affiliations

To the Editor:

We read with great interest the recent article by Lew and colleagues[1] dealing with the relationship between estrogens and endothelial function in men. The results of their study demonstrated that the suppression of endogenous estrogens with an aromatase inhibitor, anastrozole, resulted in impairment of flow-mediated dilatation of the brachial artery in healthy young men. The authors proposed that estrogens might play a direct regulatory role in endothelial function not only in women but also in men.

There is evidence that estrogens might actively participate in the regulation of membrane function. Whiting et al[2] demonstrated the nongenomic effects of steroid hormones on phosphatidylcholine liposome, synaptosomal plasma membranes, and sarcoplasmic reticulum membranes. In the studies we presented earlier, a relationship between membrane fluidity (a reciprocal value of membrane microviscosity) of erythrocytes and estrogens was investigated by means of an electron paramagnetic resonance method. The decreased membrane fluidity of erythrocytes might cause a disturbance in the blood rheologic behavior and the microcirculation, which could contribute, at least in part, to the pathophysiology of circulatory disorders. We demonstrated that hormone (estrogen) replacement therapy significantly increased the membrane fluidity of erythrocytes with a concomitant increase in plasma nitric oxide (NO) metabolite level in postmenopausal women.[3] In an in vitro study, we showed that 17β-estradiol, estrone, and estriol increased the membrane fluidity of erythrocytes and improved the rigidity of cell membranes via the NO- and cGMP-dependent mechanism not only in women but also in men.[4-6] One hypothesis is that the membrane action of estrogens could be one of the mechanisms responsible for their beneficial effects on the rheologic properties of erythrocyte membranes. In this context, we speculate that estrogen-induced NO production might modulate the membrane microviscosity both in men and women, which could partially explain the preventing effect of estrogens against the vascular complications. It would be necessary to assess more precisely the functional interactions between estrogens and NO in the regulation of membrane microviscosity and their contribution to the vascular function both in men and women.

1 of 2 7/8/2012 5:09 PM

- This study demonstrated that the suppression of endogenous estrogens with an aromatase inhibitor, anastrozole, results in impairment of flow-mediated dilatation of the brachial artery in healthy young men.
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Tsuda K, Nishio I. Role of estrogens in the regulation of membrane microviscosity. *Circ Res*. 2004 Feb 6;94(2):e17.

Physiological levels of estradiol stimulate plasma high density lipoprotein2 cholesterol levels in normal men.

Physiological levels of estradiol stimulate plasma high density lipopr... http://jcem.endojournals.org/content/78/4/855.abstract

Journal of Clinical Endocrinology & Metabolism
jcem.endojournals.org

doi: 10.1210/jc.78.4.855
The Journal of Clinical Endocrinology & Metabolism April 1, 1994 vol. 78 no. 4 855-861

Home | 1994 Archive | April 1994 | Bagatell et al. 78 (4): 855

Physiological levels of estradiol stimulate plasma high density lipoprotein2 cholesterol levels in normal men.

C J Bagatell, R H Knopp, J E Rivier and W J Bremner

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Medical Service, Seattle Veterans Affairs Medical Center, Washington 98108.

Abstract

Premenopausal women have a lower risk of coronary artery disease than men or postmenopausal women; estrogens are thought to contribute to this lower risk. Administration of exogenous estrogen to post-menopausal women increases plasma high density lipoprotein (HDL) cholesterol and may reduce mortality from coronary disease in users. Although many investigations have examined the roles of estrogen in the regulation of lipoproteins in women, little attention has been directed to estrogen regulation of lipids in men. We designed a paradigm to study the role of physiological levels of estradiol (E2) on plasma lipoproteins in healthy men. We used a GnRH antagonist, Nal-Glu, to suppress endogenous steroid hormones in healthy men. We then administered testosterone (T) enanthate (100 mg, im, weekly) to restore T levels to the baseline range, and we administered an aromatase inhibitor, testolactone (Teslac), to prevent the normal conversion of T to E2, thereby producing a selective estrogen deficiency state in normal young men. As controls, we administered Nal-Glu and T along with placebo Teslac to a separate group of men; a third group of men received all placebo medications. We found that in men who received Nal-Glu plus T plus Teslac, E2 levels were profoundly suppressed during treatment, whereas T levels remained in the baseline range. Plasma HDL cholesterol, particularly, the HDL2 fraction, decreased significantly in response to the low serum E2 level. Plasma apoprotein-AI levels also decreased significantly. Plasma LDL and triglyceride levels did not change. All hormone and lipoprotein parameters returned to baseline within 4 weeks after treatment ended. In men who received Nal-Glu plus T, plasma HDL and apoprotein-AI decreased, but these decreases did not achieve statistical significance. Only a small decrease in HDL2 cholesterol was seen in these men. There were no hormonal or lipid changes in the placebo group. We conclude that in men, physiological levels of E2 are important in maintaining plasma levels of HDL cholesterol, especially the HDL2 fraction. These observations suggest that estrogen, in the amount normally produced in men, may offer some degree of protection against cardiovascular disease in males, as they do in women.

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Bagatell CJ, Knopp RH, Rivier JE, Bremner WJ. Physiological levels of estradiol stimulate plasma high density lipoprotein2 cholesterol levels in normal men. *J Clin Endocrinol Metab*. 1994 Apr;78(4):855-61.

Physiological levels of estradiol stimulate plasma high density lipoprotein2 cholesterol levels in normal men.

Physiological levels of estradiol stimulate plasma high density lipopr... http://jcem.endojournals.org/content/78/4/855.abstract

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Physiological levels of estradiol stimulate plasma high density lipoprotein2 cholesterol levels in normal men.

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Estrogens and Cardiovascular Disease in the Male

Estrogens and Cardiovascular Disease in the Male | Revista Española... http://www.revespcardiol.org/pt/node/2058292

Estrogens and Cardiovascular Disease in the Male

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Artículo

To the Editor:

The role of estrogens in the prevention of cardiovascular disease is currently of particular interest. Recently, Wenger[1] reviewed various randomized clinical trials to assess the effect of hormone replacement therapy in cardiovascular disease and concluded that postmenopausal hormone therapy does not prevent clinical cardiovascular events in healthy women or women with heart disease. The question remains to be fully resolved, however, since the effect of treatment with estrogens at an earlier stage, at different dosages, or via other routes of administration is still not known. Clinical and experimental evidence is also available that obliges us to consider the role of estrogens in cardiovascular disease in men.

Although the precise actions of estrogens are not well known, they are thought to be essential for correct male development, as is apparent from rare cases of estrogen deficiency, caused by a defective aromatase enzyme, or estrogen resistance due to abnormalities of the cellular estrogen receptor. Phenotypically, they have been associated with osteoporosis, tallness, delayed epiphyseal closure, genu valgum, and eunuchoid proportions; metabolically, they are associated with changes in lipid profile, hyperglycemia, and insulin resistance. These manifestations vary according to the mechanism underlying the reduction in estrogen activity: in a patient with estrogen resistance, low levels of high-density lipoprotein (HDL-C) cholesterol were observed along with low levels of low-density lipoprotein (LDL-C) cholesterol and normal levels of triglycerides (TG), while in men with aromatase deficiency low levels of HDL-C have been observed along with high levels of LDL-C and TG.[2] In healthy men, estradiol level is associated with levels of apolipoprotein E and regulation of systolic and diastolic blood pressure. In addition, it acts along with testosterone to maintain normal levels of insulin sensitivity. The effects of estrogens can also be explained by their action as regulators of nitric oxide.[3]

The results of animal studies, as in humans, have been disparate. While in young men estradiol levels are negatively correlated with LDL-C and fasting glucose levels, a later study found no relationship between different cardiovascular risk factors and estrogens.[4,5] In a prospective cohort study in men in which the relationship between circulating sex hormones and cardiovascular disease was assessed, an association was observed between elevated levels of estradiol and reduced risk of disease for men older than 56 years, without a significant association with male sex hormones, although a cardioprotective effect for those hormones could not be ruled out.[6] In healthy men of fertile age subjected to estrogen suppression, a reduction was observed in plasma levels of HDL-C, particularly fraction 2, and a significant reduction in flow-mediated vasodilation.[7,8] Estrogen supplementation in healthy men aged more than 65 years reduces the levels of homocysteine, fibrinogen, and plasminogen activator inhibitor (PAI), and has a favorable effect on very low-density lipoprotein (VLDL-C) cholesterol, LDL-C, and HDL-C. In young men, vascular reactivity (flow-mediated vasodilation) is greater in those receiving estrogens and testosterone than in those receiving testosterone alone.[9] A reduction in the vasoconstrictor response to substances such as angiotensin II and noradrenaline has also been observed.[10] In contrast, an earlier study found no change in vessel diameter in older men following estrogen supplementation, whereas a change was observed in postmenopausal women of a similar age.[11] In transsexuals receiving chronic estrogen therapy, it has been observed that there is greater vascular reactivity than in control subjects, as well as increased levels of HDL-C and TG, increased visceral and subcutaneous fat, and reduced LDL-C levels, LDL-C particle size, and insulin sensitivity.[12,13] These conflicting results may be explained by the different doses of estrogens used in the studies and the use or not of antiandrogens, which would abrogate the possible influence of testosterone.

There is experimental and clinical evidence supporting a beneficial effect of estrogens in men, despite the presence in some studies of conflicting results, which may be explained by the study characteristics. More data is needed on the physiologic levels of estrogens in men, their physiologic effects, and the cardiovascular effects of estrogen supplementation in order to assess their usefulness in the prevention and treatment of atherosclerotic disease.

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- In men with aromatase deficiency low levels of HDL-C have been observed along with high levels of LDL-C and TG. In healthy men, estradiol level is positively associated with levels of apolipoprotein A and regulation of systolic and diastolic blood pressure.
- It acts along with testosterone to maintain normal levels of insulin sensitivity. The effects of estrogens can also be explained by their action as regulators of nitric oxide.
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Fleta-Asin, B. (2012). Estrogens and Cardiovascular Disease in the Male.

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- In healthy men subjected to estrogen suppression a reduction was observed in plasma levels of HDL-C, particularly fraction 2 and a significant reduction in flow-mediated vasodilation.
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- Vascular reactivity is greater in those receiving estrogens and testosterone than in those receiving testosterone alone.

Effects of Aromatase Inhibition on Bone Mineral Density and Bone Turnover in Older Men with Low Testosterone Levels

Effects of Aromatase Inhibition on Bone Mineral Density and Bone T... http://jcem.endojournals.org/content/94/12/4785.abstract

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Home | 2009 Archive | December 2009 | Burnett-Bowie et al. 94 (12): 4785

ENDOCRINE CARE

Effects of Aromatase Inhibition on Bone Mineral Density and Bone Turnover in Older Men with Low Testosterone Levels

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Abstract

Context: Aging is associated with declining gonadal steroid production, low bone mineral density (BMD), and fragility fractures. The efficacy and safety of testosterone replacement in older men remains uncertain.

Objective: The objective of the study was to assess the effects of aromatase inhibition on BMD in older men with low testosterone levels.

Design and Setting: This was a 1-yr, double-blind, randomized, placebo-controlled trial that was conducted at a tertiary care academic center in Boston, MA.

Participants: Participants included 69 men aged 60+ yr with borderline or low testosterone levels and hypogonadal symptoms.

Intervention: Intervention included 1 mg anastrozole daily or placebo.

Main Outcome Measures: Changes in gonadal steroid hormone levels, BMD, and bone turnover markers were measured.

Results: Mean serum testosterone increased from 319 ± 93 ng/dl at baseline to 524±136 ng/dl at month 3 ($P < 0.0001$) and declined slightly to 474 ± 145 ng/dl by 1 yr. Estradiol levels decreased from 16 ± 4 pg/ml at baseline to 12 ± 4 pg/ml at month 3 and then remained stable ($P < 0.0001$). Posterior-anterior (PA) spine BMD decreased in the anastrozole group as compared with placebo ($P = 0.0014$). In the anastrozole group, PA spine BMD decreased from 1.121 ± 0.141 g/cm^2 to 1.102 ± 0.136 g/cm^2, whereas in the placebo group, PA spine BMD increased from 1.180 ± 0.145 g/cm^2 to 1.189 ± 0.146 g/cm^2. Qualitatively similar, but not statistically significant, changes occurred at the other sites. Bone turnover markers were not affected by anastrozole therapy.

Conclusions: In older men, aromatase inhibition increases testosterone levels, decreases estradiol levels, and appears to decrease BMD. Aromatase inhibition does not improve skeletal health in aging men with low or low normal testosterone levels.

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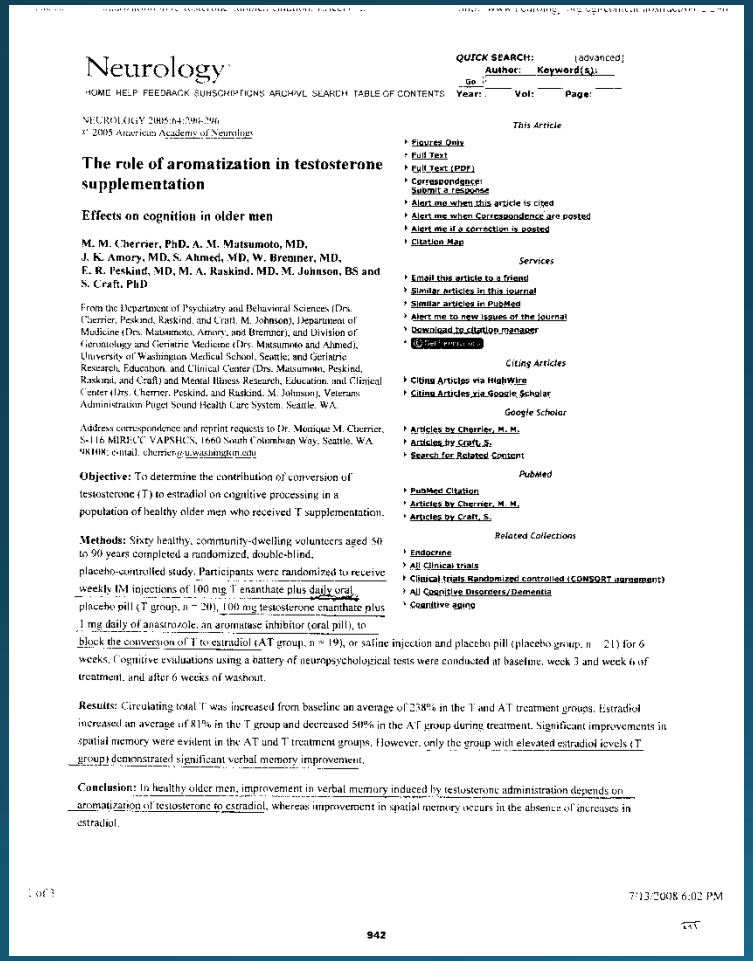
- In older men aromatase inhibition increases testosterone levels, decreased estradiol levels and appears to decrease BMD.
- Aromatase inhibition worsens skeletal health in aging men with low or low normal testosterone levels.

Burnett-Bowie, S.-A. M., McKay, E. A., Lee, H., & Leder, B. Z. (2012). Effects of Aromatase Inhibition on Bone Mineral Density and Bone Turnover in Older Men with Low Testosterone Levels. *Journal of Clinical Endocrinology & Metabolism*.

The Role Of Aromatization In Testosterone Supplementation



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NEUROLOGY 2005;64:290–296
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The role of aromatization in testosterone supplementation

Effects on cognition in older men

M. M. Cherrier, PhD, A. M. Matsumoto, MD, J. K. Amory, MD, S. Ahmed, MD, W. Bremner, MD, E. R. Peskind, MD, M. A. Raskind, MD, M. Johnson, BS and S. Craft, PhD

From the Department of Psychiatry and Behavioral Sciences (Drs. Cherrier, Peskind, Raskind, and Craft, M. Johnson), Department of Medicine (Drs. Matsumoto, Amory, and Bremner), and Division of Gerontology and Geriatric Medicine (Drs. Matsumoto and Ahmed), University of Washington Medical School, Seattle; and Geriatric Research, Education, and Clinical Center (Drs. Matsumoto, Peskind, Raskind, and Craft) and Mental Illness Research, Education, and Clinical Center (Drs. Cherrier, Peskind, and Raskind, M. Johnson), Veterans Administration Puget Sound Health Care System, Seattle, WA.

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Objective: To determine the contribution of conversion of testosterone (T) to estradiol on cognitive processing in a population of healthy older men who received T supplementation.

Methods: Sixty healthy, community-dwelling volunteers aged 50 to 90 years completed a randomized, double-blind, placebo-controlled study. Participants were randomized to receive weekly IM injections of 100 mg T enanthate plus daily oral placebo pill (T group, n = 20), 100 mg testosterone enanthate plus 1 mg daily of anastrozole, an aromatase inhibitor (oral pill), to block the conversion of T to estradiol (AT group, n = 19), or saline injection and placebo pill (placebo group, n = 21) for 6 weeks. Cognitive evaluations using a battery of neuropsychological tests were conducted at baseline, week 3 and week 6 of treatment, and after 6 weeks of washout.

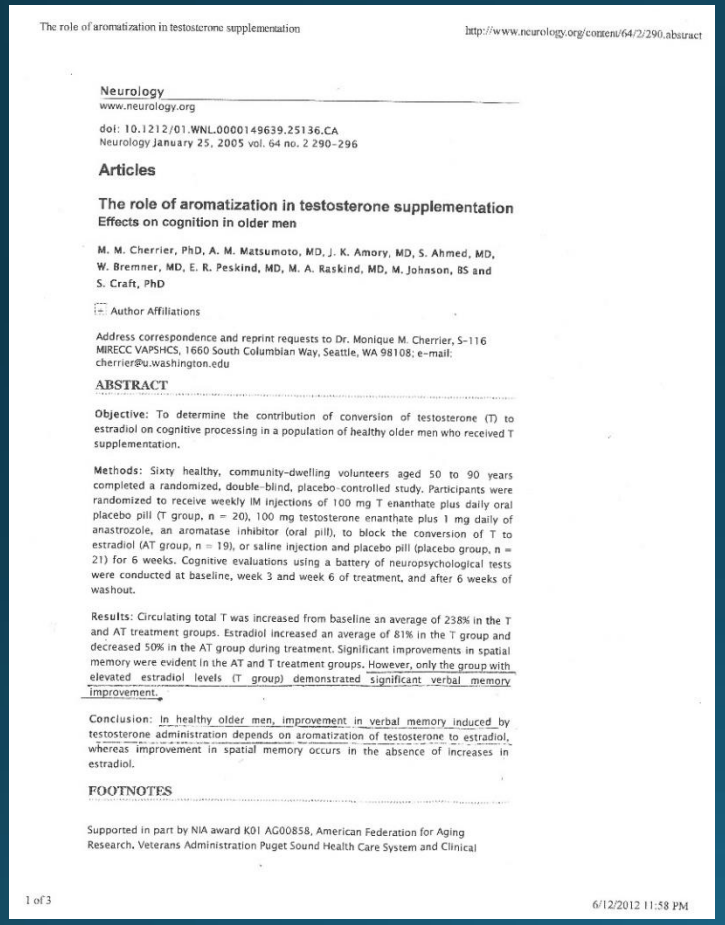
Results: Circulating total T was increased from baseline an average of 238% in the T and AT treatment groups. Estradiol increased an average of 81% in the T group and decreased 50% in the AT group during treatment. Significant improvements in spatial memory were evident in the AT and T treatment groups. However, only the group with elevated estradiol levels (T group) demonstrated significant verbal memory improvement.

Conclusion: In healthy older men, improvement in verbal memory induced by testosterone administration depends on aromatization of testosterone to estradiol, whereas improvement in spatial memory occurs in the absence of increases in estradiol.

- Participants were randomized to receive weekly IM injections of 100 mg T enanthate or 100 mg testosterone enanthate plus 1 mg daily of anastrozole, an aromatase inhibitor (oral pill), to block the conversion of T to estradiol.

Cherrier MM, Matsumoto AM, Amory JK, et al. The role of aromatization in testosterone supplementation: effects on cognition in older men. Neurology. 2005 Jan 25;64(2):290-6.

The role of aromatization in testosterone supplementation. Effects on cognition in older men.



The role of aromatization in testosterone supplementation http://www.neurology.org/content/64/2/290.abstract

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Articles

The role of aromatization in testosterone supplementation
Effects on cognition in older men

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ABSTRACT

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FOOTNOTES

Supported in part by NIA award K01 AG00858, American Federation for Aging Research, Veterans Administration Puget Sound Health Care System and Clinical

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- However, only the group with elevated estradiol levels (T group and no arimidex) demonstrated significant verbal memory improvement.
- In healthy older men, improvement in verbal memory induced by testosterone administration depends on aromatization of testosterone to estradiol.

Cherrier, PhD, M. M., Matsumoto, MD, A. M., Amory, MD, J. K., Ahmed, MD, S., Bremner, MD, W., Peskind, MD, E. R., . . . Craft, PhD, S. (2005). The role of aromatization in testosterone supplementation Effects on cognition in older men. *Neurology*.

Testosterone: More Is Not Always Better

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EDITORIAL

Testosterone: More Is Not Always Better

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Having conducted population-based studies on the relationship of sex steroid levels to bone mass in Rochester, Minnesota for many years, I have been struck by just how often male members of the medical staff at our institution who participate in these studies inquire about their testosterone level. Discovering that they happen to be in the top 10th percentile is often a cause for celebration; conversely, being told that they happen to be "average" or, most distressingly, "below average," generally leads to at least temporary anguish. Not surprisingly, despite the numerous publications from our group and others regarding the key role for estrogen in bone metabolism in men (summarized in Ref. 1), none of my colleagues inquire or seem to care one way or another about their estradiol level. At least based on this anecdotal experience, it seems that even in the minds of well-informed male medical professionals, more testosterone is clearly "better," whereas estrogen is largely irrelevant.

It is in this context that men with modest testosterone levels should perhaps have their chance to celebrate based on the results of the study by Burnett-Bowie *et al.* (2) published in this issue of *JCEM*. This carefully conducted clinical trial clearly demonstrates that at least for bone, more testosterone is not necessarily better, especially if it comes at the price of lower estrogen production.

The trial is based on the premise that because male aging is associated with declining testosterone levels and with increased body fat, decreased muscle mass, strength, and bone mineral density (BMD) (1), replacing testosterone in elderly men should be beneficial. However, rather than administering exogenous testosterone, which requires topical or parenteral dosing and significantly increases estrogen levels (via peripheral aromatization) and which may, in turn, result in side effects such as gynecomastia, the authors chose to test the effects of increasing endogenous testosterone production by blocking aromatization of testosterone to estradiol using a potent orally administered aromatase inhibitor, anastrozole (2). By removing negative feedback signals, the anastrozole-induced decrease in estradiol increases GnRH and gonadotropin production at the hypothalamus and pituitary, respectively, thereby increasing testosterone production (3).

The Burnett-Bowie *et al.* (2) paper reports on 69 men, aged 60 and older, who completed the 1-yr, double-blind, randomized, placebo-controlled trial. Anastrozole had the desired effects on serum testosterone levels, with mean values increasing from 319 ng/dl (the lower end of the normal range) at baseline to 524 ng/dl at 3 months and a slight decline to 474 ng/dl at 1 yr, an overall increase of approximately 50%. As expected, estradiol levels decreased (by 20%), from 15 to 12 pg/ml at 3

- Despite the numerous publications from our group and others regarding the key role of estrogen in bone metabolism in men, none of my colleagues inquire or seem to care one way or another about their estradiol levels.
- At least based on this anecdotal experience, it seems that even in the minds of well-informed male medical professionals, more testosterone is clearly "better," whereas estrogen is largely irrelevant.

Khosia, S. (2009). Testosterone: More Is Not Always Better. *Journal of Clinical Endocrinology & Metabolism*.

Testosterone: More Is Not Always Better

Testosterone: More Is Not Always Better http://jcem.endojournals.org/content/94/12/4665.full

months, and remained stable at this level thereafter. However, despite the substantial increase in serum testosterone levels, posterior-anterior (PA) spine BMD decreased by 1.7% in the anastrozole group while increasing by 0.8% in the placebo group ($P = 0.0014$ for the difference between groups), with similar trends for differences between the groups for femoral neck, total hip, and total body BMD. The inescapable conclusion from these data is that the 50% increase in testosterone levels was trumped by the much more modest 20% reduction in estradiol levels, leading to negative skeletal effects of anastrozole therapy in aging men.

To some extent, these findings are not surprising and are perhaps predictable, based on the now extensive body of evidence for a critical role for estrogen in regulating the male skeleton (1). Although previous studies in men had shown that serum estradiol levels were related to bone density (4) and that estrogen regulated bone turnover (5, 6) and bone loss (7) in elderly men, more recent studies have now also demonstrated that serum estradiol, and not serum testosterone, levels are the most robust hormonal predictors of fracture risk in aging men (8, 9, 10). What is perhaps somewhat surprising from the study of Burnett-Bowie *et al.* (2) is that relatively small reductions in estradiol levels appear to significantly modulate rates of bone loss. Although this may reflect just how heavily leveraged the male skeleton is on circulating estrogen levels, an alternate explanation for this finding is that changes in serum estradiol levels may not fully reflect reductions in local estrogen production in osteoblastic cells (11), and the extent of skeletal estrogen deficiency induced by anastrozole may therefore be underestimated by serum estradiol measurements.

It is also perhaps somewhat surprising that despite a fairly consistent pattern of changes in BMD at various sites, anastrozole treatment did not alter markers of bone formation or resorption (2). Because other studies have shown that estrogen clearly suppresses bone resorption in men and is also critical for the maintenance of bone formation (5), the lack of change in bone turnover markers may reflect the relative insensitivity of these markers to a subtle imbalance between bone resorption and bone formation induced by aromatase inhibition, which nonetheless resulted in measurable bone loss even over just 1 yr.

The findings of Burnett-Bowie *et al.* (2) also need to be placed in the context of previous trials of testosterone replacement in older men. Thus, Amory *et al.* (12) found that 200 mg of im testosterone every 2 wk increased spine BMD by 10% and total hip BMD by 3%. By contrast, effects of transdermal testosterone on bone density have been marginal (13), suggesting that the higher testosterone levels associated with im treatment may be necessary for achieving beneficial skeletal effects. Based on the evidence provided by Burnett-Bowie *et al.* (2), it is probable that it is the higher estradiol levels associated with the higher testosterone levels (rather than the testosterone levels themselves) that are necessary for optimal skeletal benefits.

In the same study of im testosterone noted above, Page *et al.* (14) also found that testosterone therapy was associated with beneficial changes in body composition, including an increase in lean mass and a decrease in fat mass. Interestingly, a previous report by Burnett-Bowie *et al.* (3) using body composition data from the same anastrozole trial found no effect of anastrozole on either lean or fat mass. This finding raises the question of whether the body composition changes associated with testosterone therapy may also be mediated, at least in part, via aromatization to estradiol. As noted by the authors in their previous publication (3), there is evidence from rodent and human studies supporting a role for estrogen in regulating body composition. Thus, male mice with inactivation of either estrogen receptor α or the aromatase genes have increased fat mass (15, 16). Moreover, Vandenput *et al.* (17) found that in orchidectomized rats, estradiol not only prevented bone loss but also increased lean body mass and inhibited the orchiectomy-associated increase in fat mass. Studies in men with prostate cancer have found that treatment with bicalutamide (an androgen receptor blocker that increases estradiol levels) results in smaller increases in fat mass compared with treatment with a GnRH agonist (which reduces both testosterone and estradiol production) (18). Combined with the data from the anastrozole study (3), these findings indicate that aromatization of testosterone to estradiol may be critical not only for skeletal preservation but also for beneficial

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- BMD decreased by 1.7% in the anastrozole treated group.
- The 50% increase in testosterone levels was trumped by the much more modest 20% reduction in estradiol levels, leading to negative skeletal effects of anastrozole therapy in aging men.
- More recent studies have now also demonstrated that serum estradiol and not serum testosterone levels are the most robust hormonal predictors of fracture risk in aging men.

Testosterone: More Is Not Always Better

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months, and remained stable at this level thereafter. However, despite the substantial increase in serum testosterone levels, posterior-anterior (PA) spine BMD decreased by 1.7% in the anastrozole group while increasing by 0.8% in the placebo group ($P = 0.0014$ for the difference between groups), with similar trends for differences between the groups for femoral neck, total hip, and total body BMD. The inescapable conclusion from these data is that the 50% increase in testosterone levels was trumped by the much more modest 20% reduction in estradiol levels, leading to negative skeletal effects of anastrozole therapy in aging men.

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- There is evidence for estrogen in regulating body composition.
- Estradiol not only prevented bone loss but also increased lean body mass and inhibited the orchiectomy-associated increase in fat mass.
- These findings indicate that aromatization of testosterone to estradiol may be critical not only for skeletal preservation but also for beneficial effects on body composition.

Testosterone: More Is Not Always Better

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effects on body composition.

The anastrozole data also have potential implications for the development of selective androgen receptor modulators (SARMs), which are generally not aromatized to estrogens. There is considerable pharmaceutical interest in small molecule SARMs, which activate the androgen receptor in certain tissues, such as muscle and bone, but not in other tissues, such as the prostate. While rodent studies with such compounds have shown promise (19), a caveat to be kept in mind is that whereas there is widespread expression of the aromatase enzyme in primates and in humans (*e.g.* in adipose tissues and bone), expression of aromatase is much more limited in rodents, with the major sites of expression being the gonads and the brain (20). This is reflected by the much lower serum estradiol levels in male mice (~5 pg/ml or less) (21) compared with adult men (~30 pg/ml) (7). Moreover, administration of even physiological doses of testosterone to men results in clear increases in serum estradiol levels due to peripheral aromatization of testosterone to estradiol (12); by contrast, administration of even highly pharmacological doses of testosterone fails to increase serum estradiol levels in male mice (22), due to the relatively poor peripheral aromatization of testosterone to estradiol in rodents. As such, the male rodent skeleton may have intrinsically different responses to estradiol *vs.* testosterone than the human skeleton, and findings in rodents regarding the efficacy of nonaromatizable SARMs in preventing bone loss (and perhaps in improving body composition) may not be relevant to humans. Ongoing clinical trials with these compounds should provide an answer to this important question.

In summary, whereas the concept of using an aromatase blocker to enhance endogenous testosterone production was an attractive one, it does not appear to be a viable approach for preventing age-related declines in bone mass or in improving parameters of body composition in men. These findings also suggest that as males, we should perhaps be just as interested in our estradiol levels as we seem to be in our testosterone levels, if not more so. For many reasons, however, such a dramatic change in focus seems unlikely.

Footnotes

Disclosure Summary: The author has nothing to disclose.

For article see page 4785

Abbreviations: BMD, Bone mineral density; SARM, selective androgen receptor modulator.

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Relationship of Serum Sex Steroid Levels and Bone Turnover Markers with Bone Mineral Density in Men and Women: A Key Role for Bioavailable Estrogen

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The Journal of Clinical Endocrinology & Metabolism **July 1, 1998** vol. 83 no. 7 **2266-2274**

Relationship of Serum Sex Steroid Levels and Bone Turnover Markers with Bone Mineral Density in Men and Women: A Key Role for Bioavailable Estrogen[1]

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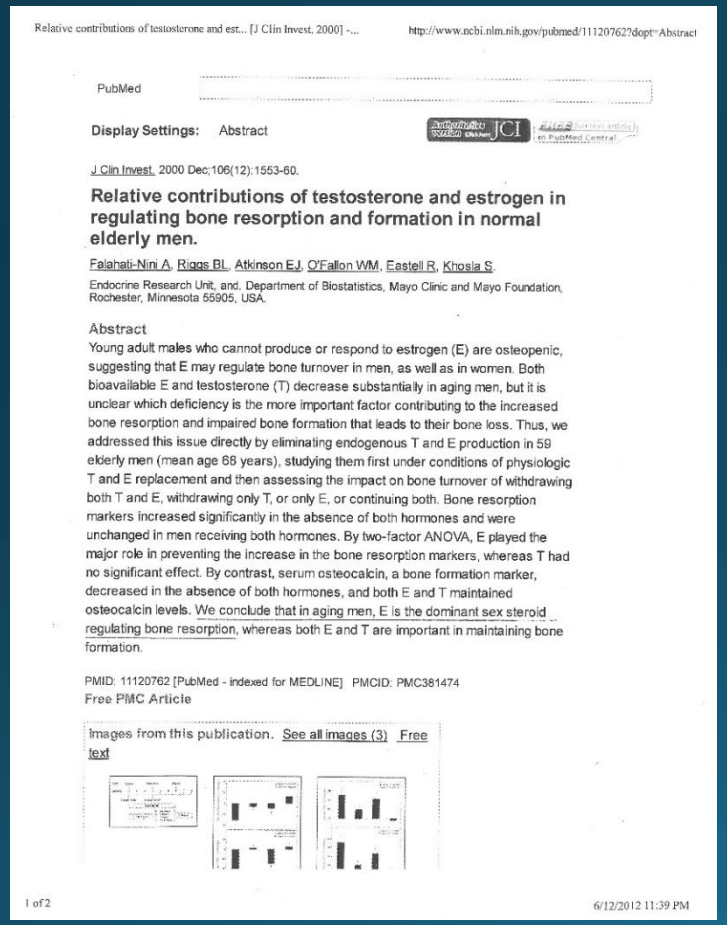
Abstract

Estrogen (E) deficiency associated with the menopause is the major cause of bone loss in aging women. However, men also lose significant amounts of bone with age, but they do not have the equivalent of menopause, and serum total testosterone (T) and E levels decline only marginally with age in men. Thus, it has been difficult to attribute bone loss in aging men to either T or E deficiency. Here, we show in a population-based, age-stratified sample of 346 men, aged 23–90 yr, that serum total T and E (estradiol plus estrone) levels decreased over the life span by 30% and 12%, respectively, but bioavailable (or nonsex hormone-binding globulin-bound) T and E levels decreased by 64% and 47%, respectively. In these men and in a parallel cohort of 304 women, aged 21–94 yr, serum PTH increased 84% and 64% over the life span, and urinary *N*-telopeptide of type I collagen (NTx) excretion, a bone resorption marker, increased 77% and 80% between age 50–85 yr in the men and women, respectively. By univariate analyses, serum bioavailable T and E levels correlated positively with bone mineral density (BMD) at the total body, spine, proximal femur, and distal radius and negatively with urinary NTx excretion in men and women. Urinary NTx excretion was also negatively associated with BMD in both sexes. By multivariate analyses, however, serum bioavailable E level was the consistent independent predictor of BMD in both men and postmenopausal women. Thus, bioavailable E levels decline significantly with age and are important predictors of BMD in men as well as women. These studies suggest that in contrast to traditional belief, age-related bone loss may be the result of E deficiency not just in postmenopausal women, but also in men.

- Estrogen level was the consistent independent predictor of BMD in both men and postmenopausal women.
- Age-related bone loss may be the result of E deficiency not just in postmenopausal women, but also in men.

Khosia, S., Melton III, L., Atkinson, E. J., O'Fallon, W., Klee, G. G., & Riggs, B. (1998). Relationship of Serum Sex Steroid Levels and Bone Turnover Markers with Bone Mineral Density in Men and Women: A Key Role for Bioavailable Estrogen. *Journal of Clinical Endocrinology & Metabolism*.

Relative contributions of testosterone and estrogen in regulating bone resorption and formation in normal elderly men.



Relative contributions of testosterone and est... [J Clin Invest. 2000] -... http://www.ncbi.nlm.nih.gov/pubmed/11120762?dopt=Abstract

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J Clin Invest. 2000 Dec;106(12):1553-60.

Relative contributions of testosterone and estrogen in regulating bone resorption and formation in normal elderly men.

Falahati-Nini A, Riggs BL, Atkinson EJ, O'Fallon WM, Eastell R, Khosla S.

Endocrine Research Unit, and. Department of Biostatistics, Mayo Clinic and Mayo Foundation, Rochester, Minnesota 55905, USA.

Abstract

Young adult males who cannot produce or respond to estrogen (E) are osteopenic, suggesting that E may regulate bone turnover in men, as well as in women. Both bioavailable E and testosterone (T) decrease substantially in aging men, but it is unclear which deficiency is the more important factor contributing to the increased bone resorption and impaired bone formation that leads to their bone loss. Thus, we addressed this issue directly by eliminating endogenous T and E production in 59 elderly men (mean age 68 years), studying them first under conditions of physiologic T and E replacement and then assessing the impact on bone turnover of withdrawing both T and E, withdrawing only T, or only E, or continuing both. Bone resorption markers increased significantly in the absence of both hormones and were unchanged in men receiving both hormones. By two-factor ANOVA, E played the major role in preventing the increase in the bone resorption markers, whereas T had no significant effect. By contrast, serum osteocalcin, a bone formation marker, decreased in the absence of both hormones, and both E and T maintained osteocalcin levels. We conclude that in aging men, E is the dominant sex steroid regulating bone resorption, whereas both E and T are important in maintaining bone formation.

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The Nonsteroidal Effects of Diethylstilbestrol: The Rationale For Androgen Deprivation Therapy Without Estrogen Deprivation in The Treatment of Prostate Cancer

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Review Article

THE NONSTEROIDAL EFFECTS OF DIETHYLSTILBESTROL: THE RATIONALE FOR ANDROGEN DEPRIVATION THERAPY WITHOUT ESTROGEN DEPRIVATION IN THE TREATMENT OF PROSTATE CANCER

DOUGLAS S. SCHERR* AND W. REID PITTS, JR.

From the James Buchanan Brady Foundation, Department of Urology, New York-Presbyterian Hospital-Weill Medical College of Cornell University, New York, New York

ABSTRACT

Purpose: During the last 2 decades there has been an increase in the number of men with prostate cancer placed on luteinizing hormone releasing hormone (LH-RH) agonist therapy. In addition, the duration of individual therapy has extended from what was once only a few months to, in many cases, several years. As a result there has been an increase in the incidence of side effects, including osteoporosis, decreased cognitive abilities, vascular stiffness and fatigue. We explored the use of estrogen in the form of diethylstilbestrol (DES) as an alternative treatment for men with prostate cancer, and introduce the concept of androgen deprivation without estrogen deprivation. In doing so we hope to elucidate some of the nonhormonal nonsteroidal effects of DES. Furthermore, we hope to define the mechanisms by which DES can be useful when LH-RH agonist therapy or orchiectomy has failed.

Materials and Methods: We comprehensively reviewed the literature from 1935 to the present regarding estrogen and antiandrogen therapy. Our search focused on issues pertaining to side effects, efficacy and nonsteroidal effects of antiandrogens and estrogens.

Results: It is readily apparent from the literature that androgen deprivation with DES can achieve effective prostate cancer control with demonstrable benefits compared to conventional LH-RH agonist therapy. In particular, rates of bone resorption and osteoporosis are less with the use of estrogen therapies. Estrogen has a clear beneficial effect on cognitive function. The estrogen metabolite 2-methoxyestradiol has significant antiangiogenic and pro-apoptotic effects. These effects give estrogens an added anticancer effect not otherwise seen in conventional LH-RH agonist therapy.

Conclusions: The efficacy of 1 mg DES extends well beyond its androgen suppressive effects. Androgen deprivation without estrogen deprivation is a concept that deserves further attention in the urological community.

KEY WORDS: diethylstilbestrol; prostatic neoplasms; androgen antagonists; estrogens, synthetic

Estrogens have represented a key component in the urological armamentarium against prostate cancer for more than 50 years. From the late 1950s through the early 1980s estrogen, in the form of diethylstilbestrol (DES), was the most used chemohormonal agent against prostate cancer. Following the initial investigative efforts of Huggins and Hodges in the early 1940s DES and surgical orchiectomy became the mainstays of androgen deprivation therapy.[1] During the ensuing 4 decades the Veterans Administration Cooperative Urological Research Group (VACURG) began their investigations into the effects of DES and hormonal deprivation therapy for prostate cancer. Although the VACURG trials were revealing in many respects, perhaps the most far-reaching message was that 5 mg DES was associated with prohibitively high cardiovascular toxicity, and 1 mg DES was equally effective without the cardiovascular effects.[2]

As this message echoed through the urological community, the luteinizing hormone releasing hormone (LH-RH) agonists began to surface as an alternative to diethylstilbestrol. Specifically, in 1984 the Leuprolide Study Group documented the effectiveness of LH-RH agonist therapy and found equal efficacy to 3 mg DES (which has greater cardiovascular toxicity than the 1 mg dose) with fewer side effects.[3] This finding ushered in the era of LH-RH agonist therapy, which proved to be well tolerated and easily administered. However, during the last 2 decades, as the number of men and the duration of therapy on LH-RH agonists have increased, a greater number of side effects have been noted. As a result the urological community is beginning to rethink its view on androgen deprivation. In particular, such effects as osteoporosis, decreased cognitive abilities, fatigue and vascular stiffness, as well as a growing rate of androgen independent prostate cancer, have turned our attention to other forms of androgen deprivation. Estrogen therapy in the form of DES

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Review Article

THE NONSTEROIDAL EFFECTS OF DIETHYLSTILBESTROL: THE RATIONALE FOR ANDROGEN DEPRIVATION THERAPY WITHOUT ESTROGEN DEPRIVATION IN THE TREATMENT OF PROSTATE CANCER

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ABSTRACT

Purpose: During the last 2 decades there has been an increase in the number of men with prostate cancer placed on luteinizing hormone releasing hormone (LH-RH) agonist therapy. In addition, the duration of individual therapy has extended from what was once only a few months to, in many cases, several years. As a result there has been an increase in the incidence of side effects, including osteoporosis, decreased cognitive abilities, vascular stiffness and fatigue. We explored the use of estrogen in the form of diethylstilbestrol (DES) as an alternative treatment for men with prostate cancer, and introduce the concept of androgen deprivation without estrogen deprivation. In doing so we hope to elucidate some of the nonhormonal nonsteroidal effects of DES. Furthermore, we hope to define the mechanisms by which DES can be useful when LH-RH agonist therapy or orchiectomy has failed.

Materials and Methods: We comprehensively reviewed the literature from 1935 to the present regarding estrogen and antiandrogen therapy. Our search focused on issues pertaining to side effects, efficacy and nonsteroidal effects of antiandrogens and estrogens.

Results: It is readily apparent from the literature that androgen deprivation with DES can achieve effective prostate cancer control with demonstrable benefits compared to conventional LH-RH agonist therapy. In particular, rates of bone resorption and osteoporosis are less with the use of estrogen therapies. Estrogen has a clear beneficial effect on cognitive function. The estrogen metabolite 2-methoxyestradiol has significant antiangiogenic and pro-apoptotic effects. These effects give estrogens an added anticancer effect not otherwise seen in conventional LH-RH agonist therapy.

Conclusions: The efficacy of 1 mg DES extends well beyond its androgen suppressive effects. Androgen deprivation without estrogen deprivation is a concept that deserves further attention in the urological community.

KEY WORDS: diethylstilbestrol; prostatic neoplasms; androgen antagonists; estrogens, synthetic

Estrogens have represented a key component in the urological armamentarium against prostate cancer for more than 50 years. From the late 1950s through the early 1980s estrogen, in the form of diethylstilbestrol (DES), was the most used chemohormonal agent against prostate cancer. Following the initial investigative efforts of Huggins and Hodges in the early 1940s DES and surgical orchiectomy became the mainstays of androgen deprivation therapy.[1] During the ensuing 4 decades the Veterans Administration Cooperative Urological Research Group (VACURG) began their investigations into the effects of DES and hormonal deprivation therapy for prostate cancer. Although the VACURG trials were revealing in many respects, perhaps the most far-reaching message was that 5 mg DES was associated with prohibitively high cardiovascular toxicity, and 1 mg DES was equally effective without the cardiovascular effects.[2]

As this message echoed through the urological community, the luteinizing hormone releasing hormone (LH-RH) agonists began to surface as an alternative to diethylstilbestrol. Specifically, in 1984 the Leuprolide Study Group documented the effectiveness of LH-RH agonist therapy and found equal efficacy to 3 mg DES (which has greater cardiovascular toxicity than the 1 mg dose) with fewer side effects.[3] This finding ushered in the era of LH-RH agonist therapy, which proved to be well tolerated and easily administered. However, during the last 2 decades, as the number of men and the duration of therapy on LH-RH agonists have increased, a greater number of side effects have been noted. As a result the urological community is beginning to rethink its view on androgen deprivation. In particular, such effects as osteoporosis, decreased cognitive abilities, fatigue and vascular stiffness, as well as a growing rate of androgen independent prostate cancer, have turned our attention to other forms of androgen deprivation. Estrogen therapy in the form of DES

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- Estrogens have an added anticancer effect not otherwise seen in conventional LH-RH agonist therapy.
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The Effect of Micronized Estradiol on Bone Turnover and Calciotropic Hormones in Older Men Receiving Hormonal Suppression Therapy for Prostate Cancer

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Original Article

The Effect of Micronized Estradiol on Bone Turnover and Calciotropic Hormones in Older Men Receiving Hormonal Suppression Therapy for Prostate Cancer

Pamela Taxel, Pamela M. Fall, Peter C. Albertsen, Robert D. Dowsett, Margaret Trahiotis, Jill Zimmerman, Christine Ohannessian and Lawrence G. Raisz

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Abstract

To examine the effect of estradiol (E_2) without the confounding effect of hypothalamic-pituitary feedback, we studied men with prostate cancer in whom gonadotropin secretion was suppressed by LH-releasing hormone agonists (LHRH-A). Fourteen men over 65 yr of age and receiving established LHRH-A treatment (EST group) without bony metastases and 12 men who received LHRH-A as neoadjuvant therapy for locally advanced prostate cancer (NEO group) were randomized (double blind) to receive either 1 mg/d micronized E_2 (n = 12) or placebo (PL; n = 13) for 9 wk. E_2, estrone, testosterone, SHBG, PTH, and 25-hydroxy- and 1,25-dihydroxyvitamin D levels as well as markers of bone resorption [N- and C-telopeptide cross-links (NTX and CTX) and deoxypyridinoline] and bone formation (bone-specific alkaline phosphatase, osteocalcin, and N-terminal type I collagen) were measured before LHRH-A in the NEO group, before [baseline (BL)] and after 9 wk of E_2 or PL in all patients, and 6 wk after E_2 treatment in the EST group. In the NEO group, hormone levels fell 3 wk after the initial LHRH-A injection, and deoxypyridinoline increased significantly (P = 0.006). At BL, the EST group had higher bone turnover due to the longer duration of LHRH-A treatment. With E_2 treatment, E_2 levels rose into the normal male range, and two resorption markers decreased significantly from BL by 33% for NTX (P < 0.001) and 28% for CTX (P = 0.009). Bone formation markers did not change. PTH increased by 43% from BL (P < 0.01) in the E_2 group and decreased 16% from BL in the PL group (P < 0.01). Ionized calcium did not change in the E_2 group, but increased in the PL group by 2.3% (P < 0.01). NTX and CTX increased 6 wk after E_2 withdrawal in the EST group. We conclude that E_2 inhibits bone resorption in hypogonadal men through a direct skeletal effect that is independent of PTH. Low dose estrogen may be an option for the prevention and/or treatment of bone loss in this population.

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- 1 mg/d micronized E2 was studied:
- Hormone levels fell 3 wk after the initial LHRH-A injection, and deoxypyridinoline increased significantly (indicating bone loss).
- E2 levels rose into the normal male range, and two resorption markers decreased significantly from BL by 33% for NTX (indicating no bone loss).
- We conclude that E2 inhibits bone resorption in hypogonadal men through a direct skeletal effect.
- Low dose estrogen may be an option for the prevention and/or treatment of bone loss in this population of men with prostate cancer.

Taxel, P., Fall, P. M., Albertsen, P. C., Dowsett, R. D., Trahiotis, M., Zimmerman, J., . . . Raisz, L. G. (2002). The Effect of Micronized Estradiol on Bone Turnover and Calciotropic Hormones in Older Men Receiving Hormonal Suppression Therapy for Prostate Cancer. *The Journal of Clinical Endocrinology & Metabolism*.

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Transdermal Estradiol Therapy for Advanced Prostate Cancer—Forward to the Past?

J.L. OCKRIM, E.-N. LALANI, M.E. LANIADO, S. Sr. C. CARTER, P.O. ABEL

Accepted 8 November 2002

ABSTRACT

Purpose

Current hormonal therapies for prostate cancer are associated with significant morbidities, including symptoms of andropause and osteoporosis. Oral estrogens prevented many of these problems but were abandoned due to cardiovascular toxicity attributed to hepatic effect. In contrast, parenteral estrogens prevent first pass hepatic metabolism and substantially reduce cardiovascular risk, and long-term transdermal estradiol therapy is believed to be cardioprotective. We report preliminary results of a pilot study using transdermal estradiol therapy to treat men with advanced prostate cancer.

Materials and Methods

A total of 20 patients with advanced prostate cancer were enrolled in a before and after study that examined the impact of estradiol patches on hormones, disease, thrombophilia, vascular flow, osteoporosis and quality of life.

Results

Median followup is 15 months. Estradiol levels greater than 1,000 pmol/L were achieved using 2 patches and higher levels were obtained by increasing the number of patches. All patients achieved castrate levels of testosterone within 3 weeks and had biochemical evidence of disease regression. One patient died of disease at 14 months and 1 cardiovascular complication occurred. Thrombophilic activation was avoided and vascular flow improved. Bone mineral density was significantly increased. Mild or moderate gynecomastia occurred in 80% of patients but no patient had hot flushes. All other functional and symptomatic quality of life domains improved.

Conclusions

Transdermal estradiol therapy produced an effective tumor response. Cardiovascular toxicity was substantially reduced compared with that expected of oral estrogen, and other morbidity (gynecomastia) was negligible. Transdermal estradiol therapy prevented andropause symptoms, improved quality of life scores and increased bone density. Transdermal estradiol costs a tenth of current therapy cost, with the potential for considerable economic savings over conventional hormone therapies.

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- Oral estrogens prevented many of these problems but were abandoned due to cardiovascular toxicity attributed to hepatic effect (high dose DES 5 mg).
- In contrast, parenteral estrogens prevent first pass hepatic metabolism and substantially reduce cardiovascular risk, and long-term transdermal estradiol therapy is believed to be cardioprotective.

Ockrim, J., Lalani, E., Laniaodo, M., Carter, C., & Abel, P. (2003). Transdermal Estradiol Therapy for Advanced Prostate Cancer-Forward to the Past? *The Journal of Urology*, 1735-1737.

Transdermal Estradiol Therapy for Advanced Prostate Cancer-Forward to the Past?

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ABSTRACT

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Current hormonal therapies for prostate cancer are associated with significant morbidities, including symptoms of andropause and osteoporosis. Oral estrogens prevented many of these problems but were abandoned due to cardiovascular toxicity attributed to hepatic effect. In contrast, parenteral estrogens prevent first pass hepatic metabolism and substantially reduce cardiovascular risk, and long-term transdermal estradiol therapy is believed to be cardioprotective. We report preliminary results of a pilot study using transdermal estradiol therapy to treat men with advanced prostate cancer.

Materials and Methods
A total of 20 patients with advanced prostate cancer were enrolled in a before and after study that examined the impact of estradiol patches on hormones, disease, thrombophilia, vascular flow, osteoporosis and quality of life.

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Conclusions
Transdermal estradiol therapy produced an effective tumor response. Cardiovascular toxicity was substantially reduced compared with that expected of oral estrogen, and other morbidity (gynecomastia) was negligible. Transdermal estradiol therapy prevented andropause symptoms, improved quality of life scores and increased bone density. Transdermal estradiol costs a tenth of current therapy cost, with the potential for considerable economic savings over conventional hormone therapies.

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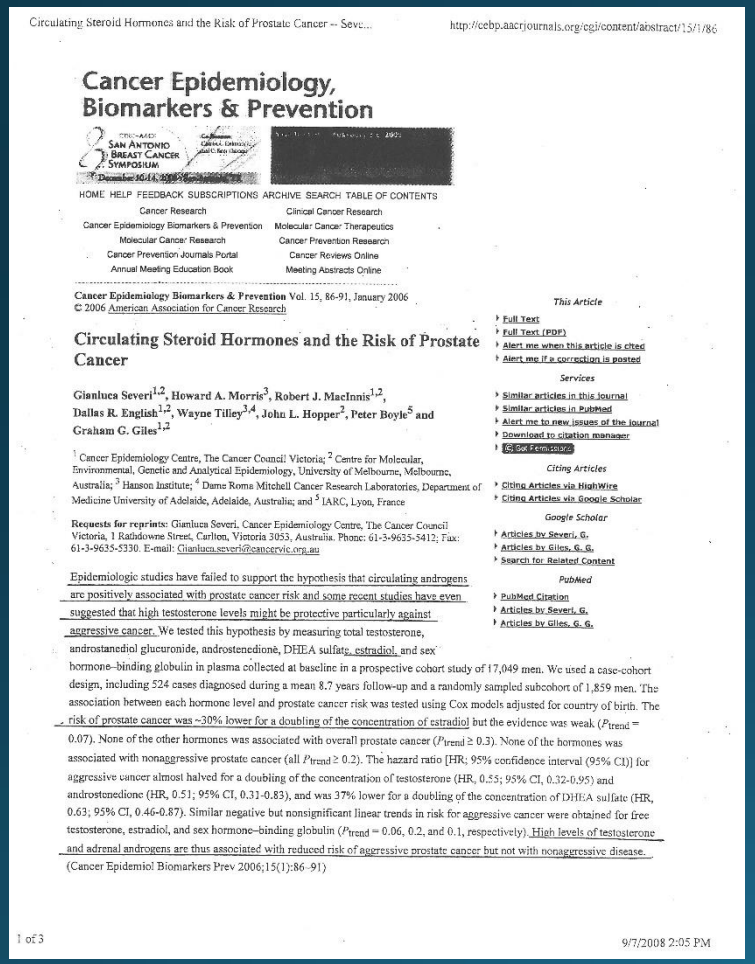
- Cardiovascular toxicity was substantially reduced compared with that expected of oral estrogen, and other morbidity (gynecomastia) was negligible.
- Transdermal estradiol therapy prevented andropause symptoms, improved quality of life scores and increased bone density.
- Transdemal estradiol costs a tenth of current LHRH therapy cost with the potential for considerable economic savings over conventional hormone therapies.

Circulating Steroid Hormones and the Risk of Prostate Cancer



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Circulating Steroid Hormones and the Risk of Prostate Cancer

Gianluca Severi[1,2], Howard A. Morris[3], Robert J. MacInnis[1,2], Dallas R. English[1,2], Wayne Tilley[3,4], John L. Hopper[2], Peter Boyle[5] and Graham G. Giles[1,2]

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Epidemiologic studies have failed to support the hypothesis that circulating androgens are positively associated with prostate cancer risk and some recent studies have even suggested that high testosterone levels might be protective particularly against aggressive cancer. We tested this hypothesis by measuring total testosterone, androstanediol glucuronide, androstenedione, DHEA sulfate, estradiol, and sex hormone–binding globulin in plasma collected at baseline in a prospective cohort study of 17,049 men. We used a case-cohort design, including 524 cases diagnosed during a mean 8.7 years follow-up and a randomly sampled subcohort of 1,859 men. The association between each hormone level and prostate cancer risk was tested using Cox models adjusted for country of birth. The risk of prostate cancer was ~30% lower for a doubling of the concentration of estradiol but the evidence was weak (P_{trend} = 0.07). None of the other hormones was associated with overall prostate cancer ($P_{trend} \geq 0.3$). None of the hormones was associated with nonaggressive prostate cancer (all $P_{trend} \geq 0.2$). The hazard ratio [HR; 95% confidence interval (95% CI)] for aggressive cancer almost halved for a doubling of the concentration of testosterone (HR, 0.55; 95% CI, 0.32-0.95) and androstenedione (HR, 0.51; 95% CI, 0.31-0.83), and was 37% lower for a doubling of the concentration of DHEA sulfate (HR, 0.63; 95% CI, 0.46-0.87). Similar negative but nonsignificant linear trends in risk for aggressive cancer were obtained for free testosterone, estradiol, and sex hormone–binding globulin (P_{trend} = 0.06, 0.2, and 0.1, respectively). High levels of testosterone and adrenal androgens are thus associated with reduced risk of aggressive prostate cancer but not with nonaggressive disease.
(Cancer Epidemiol Biomarkers Prev 2006;15(1):86–91)

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- Epidemiologic studies have failed to support the hypothesis that circulating androgens are positively associated with prostate cancer risk and some recent studies have even suggested that high testosterone levels might be protective particularly against aggressive cancer.

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Relationship of Serum Sex Steroid Levels to Longitudinal Changes in Bone Density in Young *Versus* Elderly Men

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Relationship of Serum Sex Steroid Levels to Longitudinal Changes in Bone Density in Young *Versus* Elderly Men

Sundeep Khosla, L. Joseph Melton III, Elizabeth J. Atkinson and W. M. O'Fallon

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Abstract

Estrogen appears to play an important role in determining bone mineral density in men, but it remains unclear whether estrogen primarily determines peak bone mass or also affects bone loss in elderly men. Thus, we assessed longitudinal rates of change in bone mineral density in young (22–39 yr; n = 88) *vs.* elderly (60–90 yr; n = 130) men and related these to circulating total and bioavailable estrogen and testosterone levels. In young men bone mineral density increased significantly over 4 yr at the mid-radius and ulna and at the total hip (by 0.32–0.43%/yr), whereas it decreased in the elderly men at the forearm sites (by 0.49–0.66%/yr), but did not change at the total hip. The rate of increase in bone mineral density at the forearm sites in the young men was significantly correlated to serum total and bioavailable estradiol and estrone levels (r = 0.22–0.35), but not with total or bioavailable testosterone levels. In the elderly men the rates of bone loss at the forearm sites were most closely associated with serum bioavailable estradiol levels (r = 0.29–0.33) rather than bioavailable testosterone levels. Moreover, elderly men with bioavailable estradiol levels below the median [40 pmol/liter (11 pg/ml)] had significantly higher rates of bone loss and levels of bone resorption markers than men with bioavailable estradiol levels above 40 pmol/liter. These data thus indicate that estrogen plays a key role both in the acquisition of peak bone mass in young men and in bone loss in elderly men. Moreover, our findings suggest that age-related decreases in bioavailable estradiol levels to below 40 pmol/liter may well be the major cause of bone loss in elderly men. This subset of men is perhaps most likely to benefit from preventive therapy.

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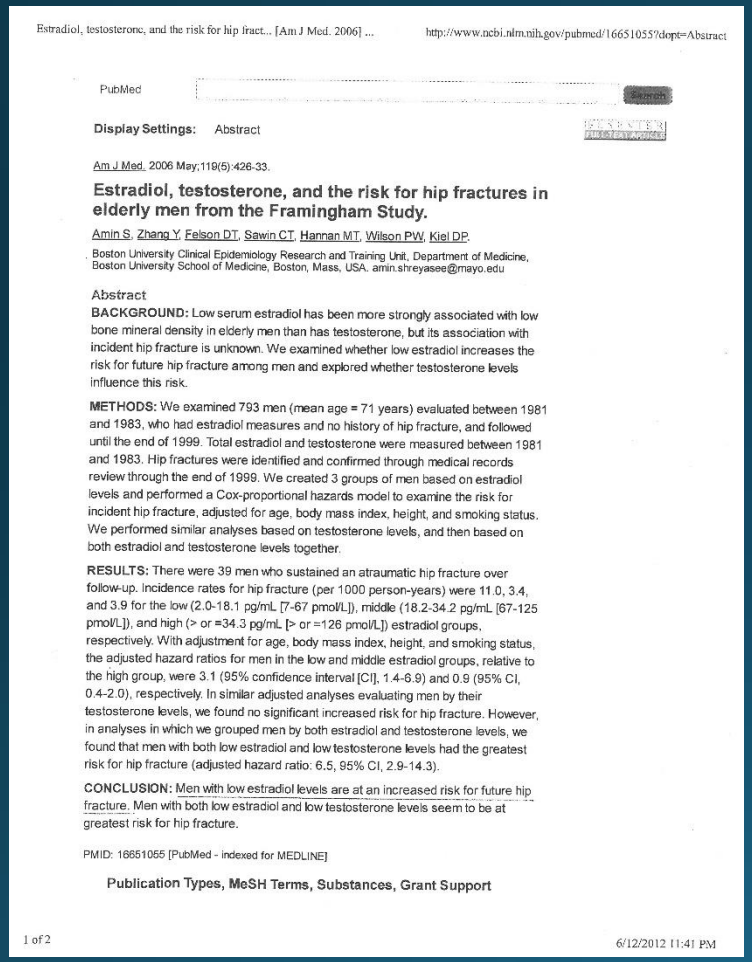
- These data thus indicate that estrogen plays a key role both in the acquisition of peak bone mass in young men and the bone loss in elderly men.
- Age-related decreases in bioavailable estradiol levels to below 40 pmol/liter may well be the major cause of bone loss in elderly men.

Khosia, S., Melton III, L., Atkinson, E. J., O'Fallon, W., Klee, G. G., & Riggs, B. (1998). Relationsihp of Serum Sex Steroid Levels and Bone Turnover Markers with Bone Mineral Density in Men and Women: A Key Role for Bioavailable Estrogen. *Journal of Clinical Endocrinology & Metabolism*.

Estradiol, testosterone, and the risk for hip fractures in elderly men from the Framingham Study.



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Am J Med. 2006 May;119(5):426-33.

Estradiol, testosterone, and the risk for hip fractures in elderly men from the Framingham Study.

Amin S, Zhang Y, Felson DT, Sawin CT, Hannan MT, Wilson PW, Kiel DP.

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Abstract

BACKGROUND: Low serum estradiol has been more strongly associated with low bone mineral density in elderly men than has testosterone, but its association with incident hip fracture is unknown. We examined whether low estradiol increases the risk for future hip fracture among men and explored whether testosterone levels influence this risk.

METHODS: We examined 793 men (mean age = 71 years) evaluated between 1981 and 1983, who had estradiol measures and no history of hip fracture, and followed until the end of 1999. Total estradiol and testosterone were measured between 1981 and 1983. Hip fractures were identified and confirmed through medical records review through the end of 1999. We created 3 groups of men based on estradiol levels and performed a Cox-proportional hazards model to examine the risk for incident hip fracture, adjusted for age, body mass index, height, and smoking status. We performed similar analyses based on testosterone levels, and then based on both estradiol and testosterone levels together.

RESULTS: There were 39 men who sustained an atraumatic hip fracture over follow-up. Incidence rates for hip fracture (per 1000 person-years) were 11.0, 3.4, and 3.9 for the low (2.0-18.1 pg/mL [7-67 pmol/L]), middle (18.2-34.2 pg/mL [67-125 pmol/L]), and high (> or =34.3 pg/mL [> or =126 pmol/L]) estradiol groups, respectively. With adjustment for age, body mass index, height, and smoking status, the adjusted hazard ratios for men in the low and middle estradiol groups, relative to the high group, were 3.1 (95% confidence interval [CI], 1.4-6.9) and 0.9 (95% CI, 0.4-2.0), respectively. In similar adjusted analyses evaluating men by their testosterone levels, we found no significant increased risk for hip fracture. However, in analyses in which we grouped men by both estradiol and testosterone levels, we found that men with both low estradiol and low testosterone levels had the greatest risk for hip fracture (adjusted hazard ratio: 6.5, 95% CI, 2.9-14.3).

CONCLUSION: Men with low estradiol levels are at an increased risk for future hip fracture. Men with both low estradiol and low testosterone levels seem to be at greatest risk for hip fracture.

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Publication Types, MeSH Terms, Substances, Grant Support

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- Men with low estradiol levels are at an increased risk for future hip fracture.

Amin, S., Qhang, Y., Felson, D., Sawin, C., Hannan, M., WIlson, P., & Kiel, D. (2006). Estradiol, Testosterone, and the risk for hip fractures in elderly men from the Framingham Study. *Am J Med*.

Low Serum Testosterone and Estradiol Predict Mortality in Elderly Men

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Low Serum Testosterone and Estradiol Predict Mortality in Elderly Men

Åsa Tivesten, Liesbeth Vandenput, Fernand Labrie, Magnus K. Karlsson, Östen Ljunggren, Dan Mellström and Claes Ohlsson

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Abstract

Context: Age-related reduction of serum testosterone may contribute to the signs and symptoms of aging, but previous studies report conflicting evidence about testosterone levels and male mortality. No large prospective cohort study has determined a possible association between serum estradiol and mortality in men.

Objective: The main objective was to examine the association between serum testosterone and estradiol and all-cause mortality in elderly men.

Design, Setting, and Participants: We used specific gas chromatography-mass spectrometry to analyze serum sex steroids at baseline in older men who participated in the prospective population-based MrOS Sweden cohort (n = 3014; mean age, 75 yr; range, 69–80 yr).

Main Outcome Measure: All-cause mortality by serum testosterone and estradiol levels.

Results: During a mean follow-up period of 4.5 yr, 383 deaths occurred. In multivariate hazards regression models, low levels (within quartile 1 *vs.* quartiles 2–4) of both testosterone [hazard ratio (HR), 1.65; 95% confidence interval (CI), 1.29–2.12] and estradiol (HR, 1.54; 95% CI, 1.22–1.95) associated with mortality. A model including both hormones showed that both low testosterone (HR, 1.46; 95% CI, 1.11–1.92) and estradiol (HR, 1.33; 95% CI, 1.02–1.73) predicted mortality. Risk of death nearly doubled (HR, 1.96; 95% CI, 1.46–2.62) in subjects with low levels of both testosterone and estradiol compared with subjects within quartiles 2–4 of both hormones.

Conclusions: Elderly men with low serum testosterone and estradiol have increased risk of mortality, and subjects with low values of both testosterone and estradiol have the highest risk of mortality.

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- Elderly men with low serum testosterone and estradiol have increased risk of mortality, and subjects with low values of both testosterone and estradiol have the highest risk of mortality.

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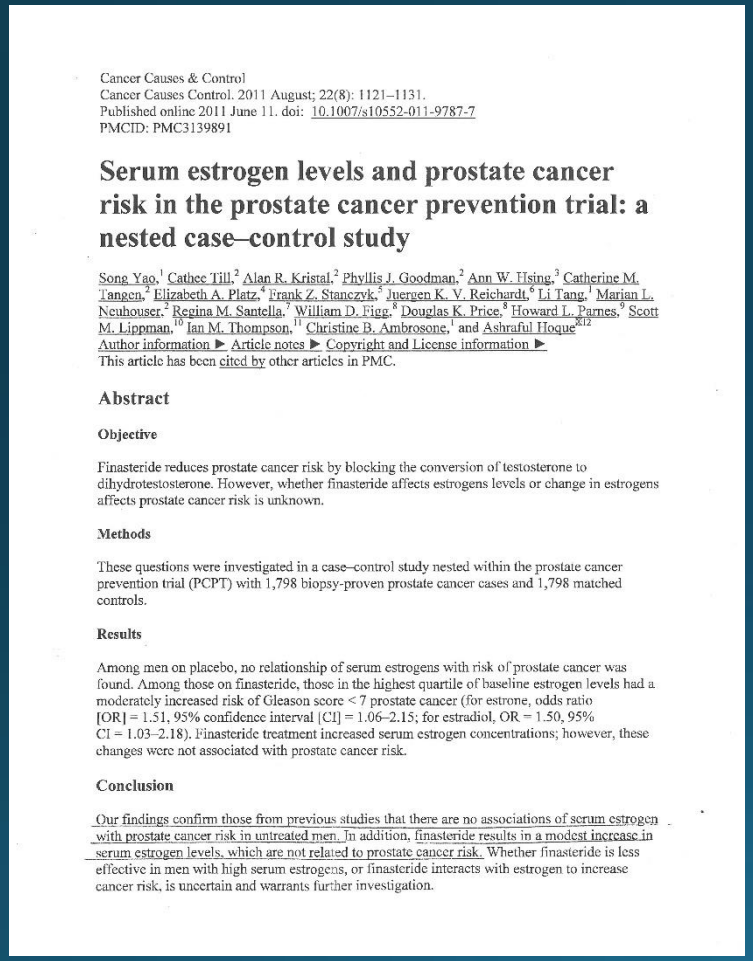
Serum estrogen levels and prostate cancer risk in the prostate cancer prevention trial: a nested case-control study



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Serum estrogen levels and prostate cancer risk in the prostate cancer prevention trial: a nested case–control study

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Abstract

Objective

Finasteride reduces prostate cancer risk by blocking the conversion of testosterone to dihydrotestosterone. However, whether finasteride affects estrogens levels or change in estrogens affects prostate cancer risk is unknown.

Methods

These questions were investigated in a case–control study nested within the prostate cancer prevention trial (PCPT) with 1,798 biopsy-proven prostate cancer cases and 1,798 matched controls.

Results

Among men on placebo, no relationship of serum estrogens with risk of prostate cancer was found. Among those on finasteride, those in the highest quartile of baseline estrogen levels had a moderately increased risk of Gleason score < 7 prostate cancer (for estrone, odds ratio [OR] = 1.51, 95% confidence interval [CI] = 1.06–2.15; for estradiol, OR = 1.50, 95% CI = 1.03–2.18). Finasteride treatment increased serum estrogen concentrations; however, these changes were not associated with prostate cancer risk.

Conclusion

Our findings confirm those from previous studies that there are no associations of serum estrogen with prostate cancer risk in untreated men. In addition, finasteride results in a modest increase in serum estrogen levels, which are not related to prostate cancer risk. Whether finasteride is less effective in men with high serum estrogens, or finasteride interacts with estrogen to increase cancer risk, is uncertain and warrants further investigation.

- Our findings confirm those from previous studies that there are no associations of serum estrogen with prostate cancer risk in untreated men.

Sex steroids and prostate carcinogenesis: integrated, multifactorial working hypothesis.

Sex steroids and prostate carcinogenesis: i... [Ann N Y Acad Sci. 200... http://www.ncbi.nlm.nih.gov/pubmed/17261765

PubMed

Display Settings: Abstract

Ann N Y Acad Sci. 2006 Nov;1089:168-76.

Sex steroids and prostate carcinogenesis: integrated, multifactorial working hypothesis.

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Abstract

Androgens are thought to cause prostate cancer, but there is little epidemiological support for this notion. Animal studies, however, demonstrate that androgens are very strong tumor promotors for prostate carcinogenesis after tumor-initiating events. Even treatment with low doses of testosterone alone can induce prostate cancer in rodents. Because testosterone can be converted to estradiol-17beta by the enzyme aromatase, expressed in human and rodent prostate, estrogen may be involved in prostate cancer induction by testosterone. When estradiol is added to testosterone treatment of rats, prostate cancer incidence is markedly increased and even a short course of estrogen treatment results in a high incidence of prostate cancer. The active testosterone metabolite 5alpha-dihydrotestosterone cannot be aromatized to estrogen and hardly induces prostate cancer, supporting a critical role of estrogen in prostate carcinogenesis. Estrogen receptors are expressed in the prostate and may mediate some or all of the effects of estrogen. However, there is also evidence that in the rodent and human prostate conversion occurs of estrogens to catecholestrogens. These can be converted to reactive intermediates that can adduct to DNA and cause generation of reactive oxygen species, and thus estradiol can be a weak DNA damaging (genotoxic) carcinogen. In the rat prostate DNA damage can result from estrogen treatment; this occurs prior to cancer development and at exactly the same location. Inflammation may be associated with prostate cancer risk, but no environmental carcinogenic risk factors have been definitively identified. We postulate that endogenous factors present in every man, sex steroids, are responsible for the high prevalence of prostate cancer in aging men, androgens acting as strong tumor promoters in the presence of a weak, but continuously present genotoxic carcinogen, estradiol-17beta.

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- When estradiol is added to testosterone treatment results in a high incidence of prostate cancer (in rats).
- We postulate that endogenous factors present in every man, sex steroids, are responsible for the high prevalence of prostate cancer in aging men, androgens acting as strong tumor promoters in the presence of a weak, but continuously present genotoxic carcinogen, estradiol- 17beta.
- Don't extrapolate rats to humans!

Bosland, M. (2006). Sex steroids and prostate carcinogenesis: intergrated, multifactorial working hypothesis. *Ann N Y Acad Sci*.

Gonadal Steroids and Body Composition, Strength, and Sexual Function in Men

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Gonadal Steroids and Body Composition, Strength, and Sexual Function in Men

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ABSTRACT

BACKGROUND

Current approaches to diagnosing testosterone deficiency do not consider the physiological consequences of various testosterone levels or whether deficiencies of testosterone, estradiol, or both account for clinical manifestations.

METHODS

We provided 198 healthy men 20 to 50 years of age with goserelin acetate (to suppress endogenous testosterone and estradiol) and randomly assigned them to receive a placebo gel or 1.25 g, 2.5 g, 5 g, or 10 g of testosterone gel daily for 16 weeks. Another 202 healthy men received goserelin acetate, placebo gel or testosterone gel, and anastrozole (to suppress the conversion of testosterone to estradiol). Changes in the percentage of body fat and in lean mass were the primary outcomes. Subcutaneous- and intraabdominal-fat areas, thigh-muscle area and strength, and sexual function were also assessed.

RESULTS

The percentage of body fat increased in groups receiving placebo or 1.25 g or 2.5 g of testosterone daily without anastrozole (mean testosterone level, 44±13 ng per deciliter, 191±78 ng per deciliter, and 337±173 ng per deciliter, respectively). Lean mass and thigh-muscle area decreased in men receiving placebo and in those receiving 1.25 g of testosterone daily without anastrozole. Leg-press strength fell only with placebo administration. In general, sexual desire declined as the testosterone dose was reduced.

CONCLUSIONS

The amount of testosterone required to maintain lean mass, fat mass, strength, and sexual function varied widely in men. Androgen deficiency accounted for decreases in lean mass, muscle size, and strength; estrogen deficiency primarily accounted for increases in body fat; and both contributed to the decline in sexual function. Our findings support changes in the approach to evaluation and management of hypogonadism in men. (Funded by the National Institutes of Health and others; ClinicalTrials.gov number, NCT00114114.)

From the Endocrine Unit, Department of Medicine (J.S.F., S.-A.M.B.-B., J.C.P., E.W.Y., L.F.B., B.F.J., C.V.B., K.E.W., B.Z.L.), Biostatistics Center (H.L.), and Department of Radiology (B.J.T.), Massachusetts General Hospital, Boston. Address reprint requests to Dr. Finkelstein at the Endocrine Unit, Thier 1051, Massachusetts General Hospital, 50 Blossom St., Boston, MA 02114, or at jfinkelstein@partners.org.

N Engl J Med 2013;369:1011-22.
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- Androgen deficiency accounted for decreases in lean mass, muscle size, and strength.
- Estrogen deficiency primarily accounted for increases in body fat; and both contributed to the decline in sexual function.

Finkelstein, MD, J. S., Lee, PhD, H., Burnett-Bowie, MD, MPH, S.-A. M., Pallais, MD, MPH, J., Yu, MD, E. W., Borges, MD, L. F., . . . Leder, MD, B. Z. (2013). Gonadal Steroids and Body Composition, Strength, and Sexual Function in Men. *The New England Journal of Medicine*.v

The NEW ENGLAND JOURNAL of MEDICINE

TESTOSTERONE THERAPY IS PRESCRIBED for millions of men each year, and the number is increasing rapidly. Prescription sales of testosterone increased by 500% in the United States between 1993 and 2000.[1] Most testosterone prescriptions are written to treat nonspecific symptoms, such as fatigue or sexual dysfunction, when accompanied by testosterone levels below the laboratory reference range. Currently, testosterone levels that are at least 2 SD below the mean value for healthy young adults are classified as low.[1,2] Although convenient, this classification fails to consider the physiological consequences of specific testosterone levels.

More than 80% of circulating estradiol in men is derived from the aromatization of testosterone.[3] Thus, as serum testosterone levels decline, there is a concomitant decline in serum estradiol levels.[4,5] Nevertheless, the consequences of male hypogonadism are routinely attributed solely to androgen deficiency; the potential role of the concomitant decline in estrogens is typically ignored. It has become clear, however, that estrogen deficiency may be important in the pathogenesis of some consequences of male hypogonadism, such as bone loss.[6-8] The potential role of estrogen deficiency in the pathogenesis of other consequences of hypogonadism, such as alterations in body composition or sexual function, is largely unknown. Information on the role of estrogens in male hypogonadism may help identify men at risk for specific manifestations of the condition and may provide a rationale for novel approaches to its management. We sought to determine the relative degree of testosterone deficiency, estradiol deficiency, or both at which undesirable changes in body composition, strength, and sexual function begin to occur and whether those changes are due to androgen deficiency, estrogen deficiency, or both.

METHODS

STUDY PARTICIPANTS

We recruited two cohorts of men who were 20 to 50 years of age and healthy. All the men had normal serum testosterone levels. Details of the eligibility criteria and study completion are provided in the Supplementary Appendix, available with the full text of this article at NEJM.org.

STUDY DESIGN AND PROTOCOL

All participants received goserelin acetate (Zoladex, AstraZeneca), at a dose of 3.6 mg subcutaneously at weeks 0, 4, 8, and 12, to suppress endogenous gonadal steroids. Participants were then randomly assigned to receive 0 g (placebo), 1.25 g, 2.5 g, 5 g, or 10 g of a topical 1% testosterone gel (AndroGel, Abbott Laboratories) daily for 16 weeks. Participants in cohort 2 also received anastrozole (Arimidex, AstraZeneca) at a dose of 1 mg daily to block the aromatization of testosterone to estrogen. Participants were unaware of the study-group assignments.

Participants were seen every 4 weeks. At each visit, fasting blood samples were obtained to measure gonadal steroid levels, and questionnaires were administered to assess physical function, health status, vitality, and sexual function. At baseline and week 16, body fat and lean mass were assessed by means of dual-energy x-ray absorptiometry (DXA); subcutaneous- and intraabdominal-fat areas and thigh-muscle area were measured by means of computed tomography (CT); and lower-extremity strength was determined by means of a leg press. Data on bone homeostasis (bone-turnover markers and bone mineral density), risk factors for cardiovascular disease (blood pressure, lipids, and insulin sensitivity), and levels of leptin and prostate-specific antigen were also collected but are not included in the present report.

The study was approved by the institutional review board of Partners HealthCare. All participants provided written informed consent. All authors vouch for the completeness and accuracy of the data and analyses and the fidelity of the study to the protocol (available at NEJM.org). All authors made the decision to submit the manuscript for publication. Abbott Laboratories provided partial financial support and supplied the testosterone gel at no charge but had no role in the study design, data analysis, data interpretation, or manuscript preparation. AstraZeneca provided Zoladex and Arimidex at no cost but had no role in the study design, data analysis, data interpretation, or manuscript preparation.

TESTOSTERONE AND ESTRADIOL MEASUREMENTS

The serum level of total testosterone was measured by means of a solid-phase chemiluminescent immunoassay with the use of an automated

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As serum testosterone levels decline, there is a concomitant decline in serum estradiol levels.

- The potential role of the concomitant decline in estrogens is typically ignored.
- Estrogen deficiency may be important in the pathogenesis of some consequences of male hypogonadism. (!!!!!)

Gonadal Steroids in Men

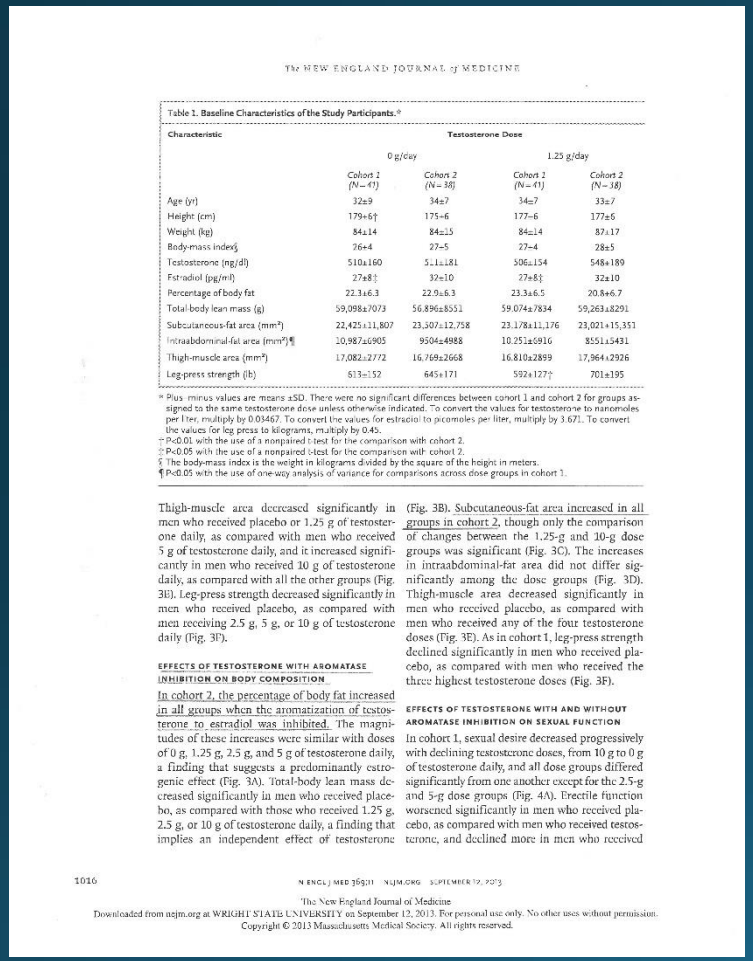


Table 1. Baseline Characteristics of the Study Participants.*

Characteristic	Testosterone Dose			
	0 g/day		1.25 g/day	
	Cohort 1 (N=41)	Cohort 2 (N=38)	Cohort 1 (N=41)	Cohort 2 (N=38)
Age (yr)	32±9	34±7	34±7	33±7
Height (cm)	179±6†	175±6	177±6	177±6
Weight (kg)	84±14	84±15	84±14	87±17
Body-mass index§	26±4	27±5	27±4	28±5
Testosterone (ng/dl)	510±160	511±181	506±154	548±189
Estradiol (pg/ml)	27±8‡	32±10	27±8‡	32±10
Percentage of body fat	22.3±6.3	22.9±6.3	23.3±6.5	20.8±6.7
Total-body lean mass (g)	59,098±7073	56,896±8551	59,074±7834	59,263±8291
Subcutaneous-fat area (mm²)	22,425±11,807	23,507±12,758	23,178±11,176	23,021±15,351
Intraabdominal-fat area (mm²)¶	10,987±6905	9504±4988	10,251±6916	8551±5431
Thigh-muscle area (mm²)	17,082±2772	16,769±2668	16,810±2899	17,964±2926
Leg-press strength (lb)	613±152	645±171	592±127†	701±195

* Plus–minus values are means ±SD. There were no significant differences between cohort 1 and cohort 2 for groups assigned to the same testosterone dose unless otherwise indicated. To convert the values for testosterone to nanomoles per liter, multiply by 0.03467. To convert the values for estradiol to picomoles per liter, multiply by 3.671. To convert the values for leg press to kilograms, multiply by 0.45.
† P<0.01 with the use of a nonpaired t-test for the comparison with cohort 2.
‡ P<0.05 with the use of a nonpaired t-test for the comparison with cohort 2.
§ The body-mass index is the weight in kilograms divided by the square of the height in meters.
¶ P<0.05 with the use of one-way analysis of variance for comparisons across dose groups in cohort 1.

Thigh-muscle area decreased significantly in men who received placebo or 1.25 g of testosterone daily, as compared with men who received 5 g of testosterone daily, and it increased significantly in men who received 10 g of testosterone daily, as compared with all the other groups (Fig. 3B). Leg-press strength decreased significantly in men who received placebo, as compared with men receiving 2.5 g, 5 g, or 10 g of testosterone daily (Fig. 3F).

EFFECTS OF TESTOSTERONE WITH AROMATASE INHIBITION ON BODY COMPOSITION

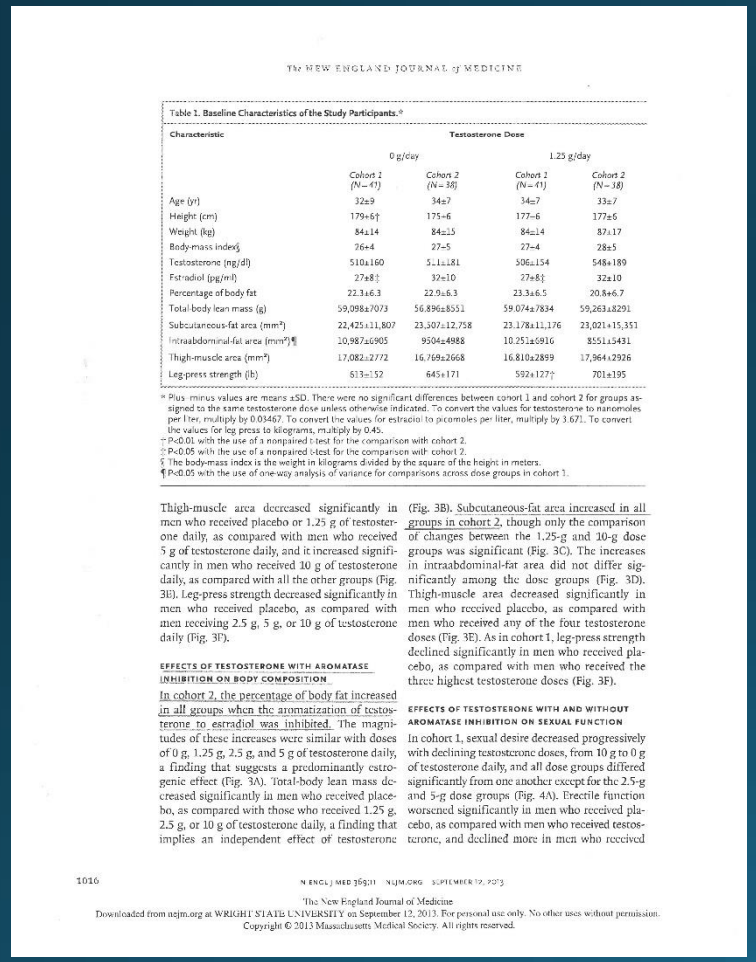
In cohort 2, the percentage of body fat increased in all groups when the aromatization of testosterone to estradiol was inhibited. The magnitudes of these increases were similar with doses of 0 g, 1.25 g, 2.5 g, and 5 g of testosterone daily, a finding that suggests a predominantly estrogenic effect (Fig. 3A). Total-body lean mass decreased significantly in men who received placebo, as compared with those who received 1.25 g, 2.5 g, or 10 g of testosterone daily, a finding that implies an independent effect of testosterone (Fig. 3B). Subcutaneous-fat area increased in all groups in cohort 2, though only the comparison of changes between the 1.25-g and 10-g dose groups was significant (Fig. 3C). The increases in intraabdominal-fat area did not differ significantly among the dose groups (Fig. 3D). Thigh-muscle area decreased significantly in men who received placebo, as compared with men who received any of the four testosterone doses (Fig. 3E). As in cohort 1, leg-press strength declined significantly in men who received placebo, as compared with men who received the three highest testosterone doses (Fig. 3F).

EFFECTS OF TESTOSTERONE WITH AND WITHOUT AROMATASE INHIBITION ON SEXUAL FUNCTION

In cohort 1, sexual desire decreased progressively with declining testosterone doses, from 10 g to 0 g of testosterone daily, and all dose groups differed significantly from one another except for the 2.5-g and 5-g dose groups (Fig. 4A). Erectile function worsened significantly in men who received placebo, as compared with men who received testosterone, and declined more in men who received

- Effects of testosterone with aromatase inhibition on body composition:
- In cohort 2, the percentage of body fat increased in all groups when the aromatization of testosterone to estradiol was inhibited.
- Subcutaneous-fat area increased in all groups in cohort 2 when estrogen was blocked!

Gonadal Steroids in Men



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- Comparisons of changes in body composition and sexual function with and without aromatase blockade:
- Inhibition of estrogen synthesis (cohort 2), as compared with intact estrogen synthesis (cohort 1), was associated with significant increases in the percentage of body fat, subcutaneous fat area, and with significant decreases in sexual desire and erectile function.

Gonadal Steroids in Men

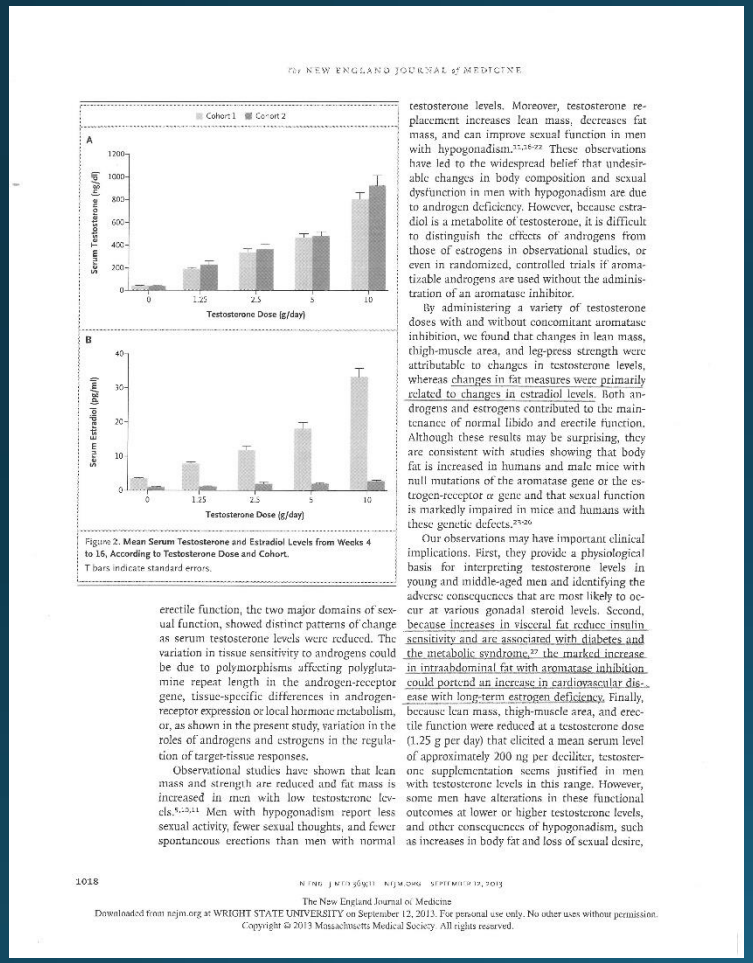


Figure 2. Mean Serum Testosterone and Estradiol Levels from Weeks 4 to 16, According to Testosterone Dose and Cohort.
T bars indicate standard errors.

erectile function, the two major domains of sexual function, showed distinct patterns of change as serum testosterone levels were reduced. The variation in tissue sensitivity to androgens could be due to polymorphisms affecting polyglutamine repeat length in the androgen-receptor gene, tissue-specific differences in androgen-receptor expression or local hormone metabolism, or, as shown in the present study, variation in the roles of androgens and estrogens in the regulation of target-tissue responses.

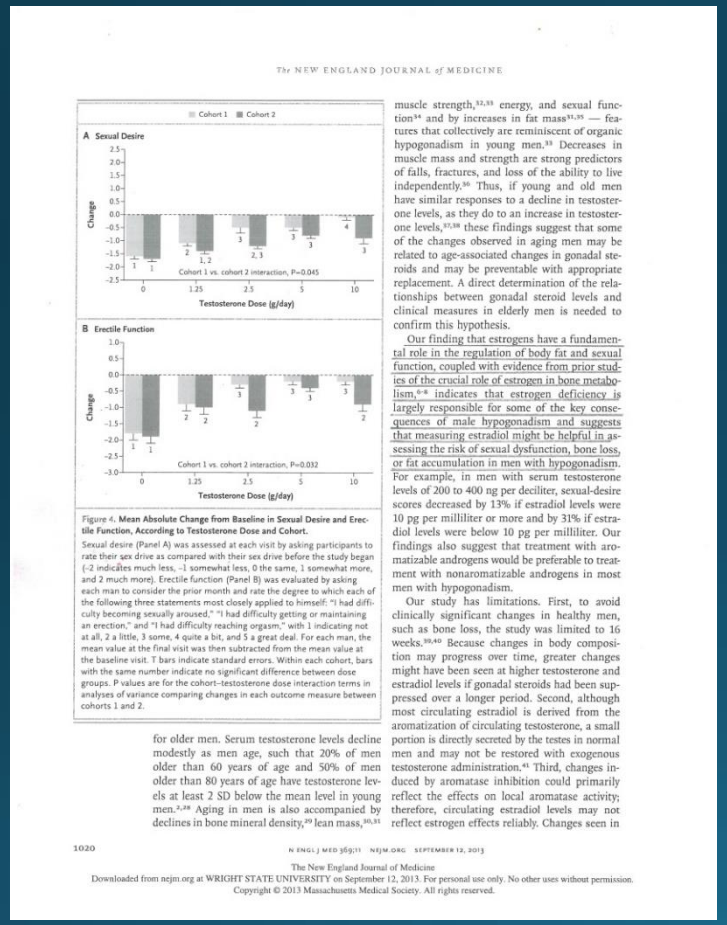
Observational studies have shown that lean mass and strength are reduced and fat mass is increased in men with low testosterone levels.[5-9,11] Men with hypogonadism report less sexual activity, fewer sexual thoughts, and fewer spontaneous erections than men with normal testosterone levels. Moreover, testosterone replacement increases lean mass, decreases fat mass, and can improve sexual function in men with hypogonadism.[17,18,22] These observations have led to the widespread belief that undesirable changes in body composition and sexual dysfunction in men with hypogonadism are due to androgen deficiency. However, because estradiol is a metabolite of testosterone, it is difficult to distinguish the effects of androgens from those of estrogens in observational studies, or even in randomized, controlled trials if aromatizable androgens are used without the administration of an aromatase inhibitor.

By administering a variety of testosterone doses with and without concomitant aromatase inhibition, we found that changes in lean mass, thigh-muscle area, and leg-press strength were attributable to changes in testosterone levels, whereas changes in fat measures were primarily related to changes in estradiol levels. Both androgens and estrogens contributed to the maintenance of normal libido and erectile function. Although these results may be surprising, they are consistent with studies showing that body fat is increased in humans and male mice with null mutations of the aromatase gene or the estrogen-receptor α gene and that sexual function is markedly impaired in mice and humans with these genetic defects.[23-26]

Our observations may have important clinical implications. First, they provide a physiological basis for interpreting testosterone levels in young and middle-aged men and identifying the adverse consequences that are most likely to occur at various gonadal steroid levels. Second, because increases in visceral fat reduce insulin sensitivity and are associated with diabetes and the metabolic syndrome,[27] the marked increase in intraabdominal fat with aromatase inhibition could portend an increase in cardiovascular disease with long-term estrogen deficiency. Finally, because lean mass, thigh-muscle area, and erectile function were reduced at a testosterone dose (1.25 g per day) that elicited a mean serum level of approximately 200 ng per deciliter, testosterone supplementation seems justified in men with testosterone levels in this range. However, some men have alterations in these functional outcomes at lower or higher testosterone levels, and other consequences of hypogonadism, such as increases in body fat and loss of sexual desire,

- Changes in fat measures were primarily related to changes in estradiol levels.
- Because increases in visceral fat reduce insulin sensitivity and are associated with diabetes and the metabolic syndrome, the marked increase in intra-abdominal fat with aromatase inhibition could portend an increase in cardiovascular disease with long-term estrogen deficiency.

Gonadal Steroids in Men



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Cohort 1 Cohort 2

A Sexual Desire

Change

Cohort 1 vs. cohort 2 interaction, P=0.045

Testosterone Dose (g/day)

B Erectile Function

Change

Cohort 1 vs. cohort 2 interaction, P=0.032

Testosterone Dose (g/day)

Figure 4. **Mean Absolute Change from Baseline in Sexual Desire and Erectile Function, According to Testosterone Dose and Cohort.**

Sexual desire (Panel A) was assessed at each visit by asking participants to rate their sex drive as compared with their sex drive before the study began (−2 indicates much less, −1 somewhat less, 0 the same, 1 somewhat more, and 2 much more). Erectile function (Panel B) was evaluated by asking each man to consider the prior month and rate the degree to which each of the following three statements most closely applied to himself: "I had difficulty becoming sexually aroused," "I had difficulty getting or maintaining an erection," and "I had difficulty reaching orgasm," with 1 indicating not at all, 2 a little, 3 some, 4 quite a bit, and 5 a great deal. For each man, the mean value at the final visit was then subtracted from the mean value at the baseline visit. T bars indicate standard errors. Within each cohort, bars with the same number indicate no significant difference between dose groups. P values are for the cohort–testosterone dose interaction terms in analyses of variance comparing changes in each outcome measure between cohorts 1 and 2.

for older men. Serum testosterone levels decline modestly as men age, such that 20% of men older than 60 years of age and 50% of men older than 80 years of age have testosterone levels at least 2 SD below the mean level in young men.[2,28] Aging in men is also accompanied by declines in bone mineral density,[29] lean mass,[30,31] muscle strength,[32,33] energy, and sexual function[34] and by increases in fat mass[31,35] — features that collectively are reminiscent of organic hypogonadism in young men.[33] Decreases in muscle mass and strength are strong predictors of falls, fractures, and loss of the ability to live independently.[36] Thus, if young and old men have similar responses to a decline in testosterone levels, as they do to an increase in testosterone levels,[37,38] these findings suggest that some of the changes observed in aging men may be related to age-associated changes in gonadal steroids and may be preventable with appropriate replacement. A direct determination of the relationships between gonadal steroid levels and clinical measures in elderly men is needed to confirm this hypothesis.

Our finding that estrogens have a fundamental role in the regulation of body fat and sexual function, coupled with evidence from prior studies of the crucial role of estrogen in bone metabolism,[6-8] indicates that estrogen deficiency is largely responsible for some of the key consequences of male hypogonadism and suggests that measuring estradiol might be helpful in assessing the risk of sexual dysfunction, bone loss, or fat accumulation in men with hypogonadism. For example, in men with serum testosterone levels of 200 to 400 ng per deciliter, sexual-desire scores decreased by 13% if estradiol levels were 10 pg per milliliter or more and by 31% if estradiol levels were below 10 pg per milliliter. Our findings also suggest that treatment with aromatizable androgens would be preferable to treatment with nonaromatizable androgens in most men with hypogonadism.

Our study has limitations. First, to avoid clinically significant changes in healthy men, such as bone loss, the study was limited to 16 weeks.[39,40] Because changes in body composition may progress over time, greater changes might have been seen at higher testosterone and estradiol levels if gonadal steroids had been suppressed over a longer period. Second, although most circulating estradiol is derived from the aromatization of circulating testosterone, a small portion is directly secreted by the testes in normal men and may not be restored with exogenous testosterone administration.[41] Third, changes induced by aromatase inhibition could primarily reflect the effects on local aromatase activity; therefore, circulating estradiol levels may not reflect estrogen effects reliably. Changes seen in

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- Our finding that estrogen has a fundamental role in the regulation of body fat and sexual function, coupled with evidence from prior studies of the crucial role of estrogen in bone metabolism, indicates that estrogen deficiency is largely responsible for some of the key consequences of male hypogonadism.
- This suggests that measuring estradiol might be helpful in assessing the risk of sexual dysfunction, bone loss, or fat accumulation in men with hypogonadism.

Estrogen receptor-β activated apoptosis in benign hyperplasia and cancer of the prostate is androgen independent and TNFα mediated

Estrogen receptor–β activated apoptosis in benign hyperplasia and cancer of the prostate is androgen independent and TNFα mediated

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Prostate cancer (PCa) and benign prostatic hyperplasia (BPH) are androgen-dependent diseases commonly treated by inhibiting androgen action. However, androgen ablation or castration fail to target androgen-independent cells implicated in disease etiology and recurrence. Mechanistically different to castration, this study shows beneficial proapoptotic actions of estrogen receptor-β (ERβ) in BPH and PCa. ERβ agonist induces apoptosis in prostatic stromal, luminal and castrate-resistant basal epithelial cells of estrogen-deficient aromatase knock-out mice. This occurs via extrinsic (caspase-8) pathways, without reducing serum hormones, and perturbs the regenerative capacity of the epithelium. TNFα knock-out mice fail to respond to ERβ agonist, demonstrating the requirement for TNFα signaling. In human tissues, ERβ agonist induces apoptosis in stroma and epithelium of xenografted BPH specimens, including in the CD133[+] enriched putative stem/progenitor cells isolated from BPH-1 cells in vitro. In PCa, ERβ causes apoptosis in Gleason Grade 7 xenografted tissues and androgen-independent cells lines (PC3 and DU145) via caspase-8. These data provide evidence of the beneficial effects of ERβ agonist on epithelium and stroma of BPH, as well as androgen-independent tumor cells implicated in recurrent disease. Our data are indicative of the therapeutic potential of ERβ agonist for treatment of PCa and/or BPH with or without androgen withdrawal.

castration | steroid receptors | selective estrogen receptor modulators

Benign prostatic hyperplasia (BPH) and prostate cancer (PCa) are the most common benign and malignant diseases in aging men (1, 2). BPH arises in the transition zone or peri-urethral glands where stromal and epithelial nodules develop, whereas PCa arises in the peripheral zone of the prostate gland where epithelial cells undergo malignant transformation. These androgen-dependent diseases are treated by inhibiting androgens or their action. In PCa, androgen ablation fails to target castrate-resistant or androgen-independent cell types, implicated in disease etiology and recurrence. Androgen blockade in men with PCa is effective initially because it causes apoptotic regression in the bulk of the tumor, although significant side effects include hypogonadism, gynecomastia, anemia, and metabolic syndrome, for which further treatments are required. Nevertheless, relapse frequently occurs, as subpopulations of cells are either castrate-resistant or adapt to androgen-deplete conditions, resulting in incurable castrate-resistant PCa (3). For BPH, anti-hormonal treatments are associated with the same side effects and often fail to permanently reduce prostatic volume or to ease lower urinary tract symptoms (4). Thus, new therapies for PCa or BPH are required that are as effective as androgen withdrawal but also target castrate-resistant cells implicated in disease recurrence.

Although estrogens were previously used for PCa therapy, their efficacy was based on indirect suppression of androgen levels; they also resulted in adverse side effects such as cardiovascular and thromboembolic events (5). It is now known that estrogens acting via ERα mediate aberrant epithelial cell proliferation, prostatic inflammation, and malignancy (6–9), and ERα antagonists such as Toremifine are in clinical trial for PCa prevention/progression (10). In contrast, effects of estrogen mediated by ERβ are beneficial; we and others previously reported anti-proliferative activity of ERβ agonist in the prostate, independent of systemic androgens (and not involving the suppression of serum testosterone) but requiring intraprostatic stromal–epithelial cell signaling (6, 11–13).

The aim of this study was to investigate the therapeutic potential of an ERβ agonist of proven selectivity (14–17), specifically investigating its proapoptotic mechanism of action compared with castration. This compound (8β-VE2) has proven selectivity and was previously used to dissect the physiological roles of ERα and ERβ in vivo in bone, cardiovascular, and metabolic studies (14–18). To circumvent the use of a specific ERβ knock-out mouse model because of reported variation in prostatic phenotypes from different colonies (19), we used aromatase knock-out (ArKO) mice that lack endogenous estrogen ligands but express functional ERs (20), thus obviating any confounding action of ER activation by endogenous ligands. Using these mice, we compared the cellular targets and mechanism of action of ERβ agonist to castration. We further verified our findings by comparing castration and ERβ agonist using human prostatic specimens and cell lines to test the therapeutic potential of ERβ agonists in PCa and BPH. Our results provide independent, unequivocal proof of the concept initially proposed by Gustafsson et al. that ERβ is anti-proliferative and proapoptotic in the prostate (13), and demonstrate a mechanism of ERβ action that is androgen-independent and mediated by TNFα, targeting castrate-resistant epithelial cells.

Results

ERβ Agonist Increases Apoptosis and Reduces Proliferation in Prostatic Stroma and Epithelia. Treatment with ERβ agonist for 6 weeks abrogated prostatic hyperplasia and hypertrophy of ArKO mice (21) because of reduced cellular proliferation; more acutely, a time course study showed that ERβ-induced apoptosis was maximal at 3–7 days, compared with the effect of an ERα agonist that causes inflammation (Fig. S1 *A* and *B*). Figure 1 shows proapoptotic effects of ERβ agonist in ArKO or wt mice within

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- Our data are indicative of the therapeutic potential of ERβ agonist for treatment of PCa and/or BPH with or without androgen withdrawal.

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- Effects of estrogen mediated by ERβ are beneficial; we and others previously reported anti-proliferative activity of ERβ agonist in the prostate, independent of systemic androgens (and not involving the suppression of serum testosterone).
- Our results provide independent, unequivocal proof of the concept that ERβ is anti-proliferative and pro-apoptotic in the prostate and demonstrate a mechanism of ERβ action that is androgen-independent.

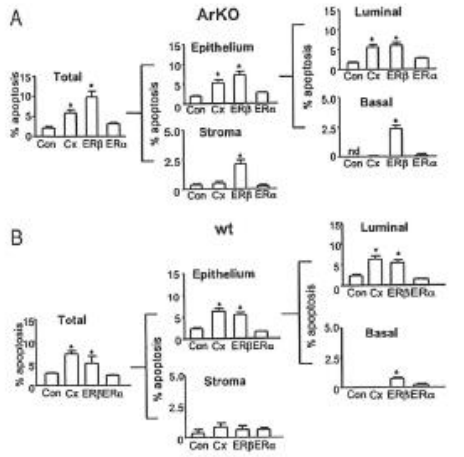

Fig. 1. Effect of selective ERβ agonist on prostatic apoptosis in ArKO (*A*) and wild-type (wt) (*B*) mice. (*A*) Apoptosis (%) in total tissue at 3 days in ArKO Control (Con), Castrate (Cx), ERβ agonist (ERβ), or ERα agonist (ERα)–treated mice. Apoptosis (%) in total tissue was subdivided into epithelial (further subdivided into luminal and basal epithelium) and stromal components. (*B*) Percentage apoptosis in total tissue at 3 days from wt Control (Con), Castrate (Cx), ERβ agonist (ERβ), or ERα agonist (ERα). Apoptosis (%) in total tissue subdivided into epithelial (luminal or basal) and stromal components. Values are mean ± SEM, $n = 5$ mice/group. nd, not detectable. *$P < 0.05$ vs. control.

3 days, compared with those in intact vehicle-treated, castrate, or ERα agonist–treated mice. Contemporary stereology and morphometric analyses show that ERβ agonist significantly increased epithelial and/or stromal apoptosis vs. vehicle controls in ArKO (Fig. 1*A*) and wt mice (Fig. 1*B*). Castration significantly increased epithelial but not stromal apoptosis, whereas ERα agonist–treated tissues showed levels of apoptosis similar to controls in all cellular compartments (Fig. 1*A* and *B*). Further subdivision into epithelial luminal and basal cells based on location and CKH immunoreactivity (basal cells are CKH-positive) showed that luminal epithelial cell apoptosis was significantly increased by both castration and ERβ agonist, but only ERβ agonist caused apoptosis of basal cells (Fig. 1*A* and *B* and Fig. S1*C*). In ArKO mice, ERβ agonist or castration (but not ERα agonist) significantly reduced epithelial (but not stromal) cell proliferation (quantified by PCNA staining) compared with controls; proliferation was reduced in luminal and basal epithelia (Fig. S2*A*). Similar results were observed in wild-type (wt) mice in which epithelial (but not stromal) cell proliferation was lowered by castration and ERβ agonist (Fig. S2*B*). Altogether, these data showed that ERβ agonist uniquely caused apoptosis in the castrate-resistant basal cell layer, reducing cell proliferation and increasing apoptosis in the luminal epithelial and stromal cells of hyperplastic and normal mouse prostate.

Epithelial Regeneration After ERβ Agonist Results in Cystic Atrophy and Depletion of p63$^+$ Basal Cells. Basal cells maintain the structural integrity of the prostatic epithelium (22) and are necessary for tissue regeneration occurring over repeated cycles of androgen deprivation and replacement. Following ERβ agonist-induced apoptosis in basal cells, we examined whether ERβ agonist treatment disrupted epithelial regenerative capacity. Twenty-one days posttreatment, ERβ agonist-treated tissues showed regions of cystic atrophy with expansion of the fluid-filled lumen (Fig. S3*A*) not seen in control or castrate-recovery tissues as evidence of perturbed glandular secretion. Prostates from castrated animals treated with androgens or intact control animal tissues showed normal morphology. The apparent frequency of p63+ cells within atrophic regions of ERβ–agonist treated tissues was reduced compared with normal control tissue but was unaltered by castration (Fig. S3*B*). Quantification of atrophy (%) and p63+ cells (p63+/100 epithelial cells) confirmed these observations, showing cystic atrophy in 42.5% of ERβ-recovered tissue within which the frequency of p63+ cells was 4.9 ± 1.4 compared with 9.8 ± 1.2 in normal regions of the same tissue (Fig S3*C*). Overall, these data show functional and structural difference between ERβ agonist and castrate tissues after recovery, because of loss of p63$^+$ basal cells. In castrate mice treated with ERβ agonist followed by 21 days of T replacement, cystic atrophy was observed in 42.6 ± 17.2% tissue within which the frequency of p63+ cells was significantly reduced (7.9 ± 0.4, compared with 12.2 ± 0.3 in normal regions of the same tissue). Therefore, regardless of androgen supplementation, ERβ agonist perturbs regeneration.

Mechanism of ERβ-Induced Apoptosis Is Androgen Independent and TNFα Mediated. To determine whether the mechanism of ERβ agonist action was androgen independent, we compared the effect of androgen supplementation on agonist-treated (ERβ+T) and castrate (Cx+T) ArKO mice. Morphometric analyses showed that testosterone supplementation did not alter the apoptotic response to ERβ agonist in any cellular compartment of the epithelium or the stroma (Fig. 2*A*). In contrast, apoptosis induced by castration was completely abrogated by testosterone supplementation (Fig. 2*A*). To demonstrate the effect of the ERβ agonist in an androgen-deplete environment, we evaluated the effect of ERβ agonist treatment on castrated (ERβ+Cx) ArKO mice. After 3 days of combined treatment, the apoptotic response to ERβ agonist was maintained (as seen in basal cells), except in stroma, where an increase in apoptosis was observed but not significant (Fig. 2*A*). Finally, although castration significantly reduced serum testosterone levels, ERβ agonist treatment showed no significant alterations in serum androgen levels (Table S1).

To identify ERβ activated gene expression, a pathway-specific DNA microarray for apoptosis was used to compare castrate and ERβ agonist–treated ArKO prostate tissues at 12 h or 3 days posttreatment. Differentially expressed genes included members of the TNF superfamily such as TNFα (Table S2). To confirm a role of TNFα signaling in ERβ agonist–induced apoptosis, we used TNFα knock-out (TNFαKO) mice after establishing normal prostatic phenotype (Fig. S4). Quantitative analysis of prostatic apoptosis (epithelial or stromal) in ERβ agonist–treated TNFαKO and wt mice showed divergent responses; TNFαKO mice failed to show any significant increase, whereas wt mice showed increased apoptosis; in contrast, castration of TNFαKO and wt mice caused the same increase in apoptosis (Fig. 2*B*).

Although extrinsic and intrinsic apoptosis pathways converge with activation of caspase-3, caspase-8 is activated through extrinsic and caspase-9 through intrinsic signaling; these cleaved caspases can differentiate between apoptotic pathways (23). Using wt mice, we showed that ERβ agonist up-regulated caspase-8, but not caspase-9 immunoreactivity, whereas castration up-regulated expression of caspase-9, but not caspase-8 in the prostate (Fig. 3*A*). Quantification of caspase immunoreactivity showed that ERβ activated apoptosis via caspase-8 in luminal, basal, and stromal cells, whereas castration activated apoptosis via caspase-9 in luminal and stromal cells but not in basal cells (Fig. 3*B*). Altogether, these data showed ERβ agonist action was mechanistically different from that of castration, independent of androgen levels as well, as activating the extrinsic apoptotic pathway in prostatic luminal and basal epithelial cells and prostatic stroma via TNFα-mediated signaling.

- Therefore, regardless of androgen supplementation, ERβ agonist perturbs regeneration.

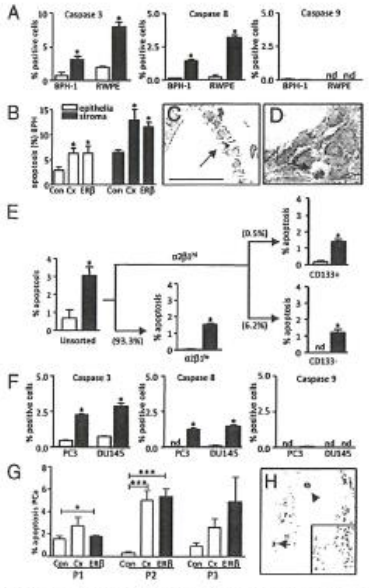

Fig. 4. ERβ agonist–induced apoptosis in human xenograft tissues and cells. (*A*) Quantification of caspase positive cells in BPH-1 and RWPE-1 cells treated with vehicle (open bars) or ERβ agonist (closed bars). (*B*) Apoptosis (%) in epithelial (open bars) and stromal (solid bars) BPH tissue xenografts ($n = 4$ patients) after 3 days treatment with control (Con), castration (Cx), or ERβ agonist (ERβ). (*C*) ApopTag staining of ERβ–treated BPH xenografts. (*D*) Morphologically identifiable apoptosis in CKH-positive basal cells. (*E*) Percent apoptosis in unsorted BPH-1 cells treated with ERβ agonist-treated (solid bars) or vehicle-treated (open bars) controls. After further fractionation to enrich for $\alpha2\beta1^{hi}$ (basal) and $\alpha2\beta1^{lo}$ (luminal) populations, $\alpha2\beta1^{hi}$ cells were sub fractionated into CD133$^+$ and CD133$^-$ subpopulations (figure representative of two individual experiments; brackets show percent cells per fraction). (*F*) Quantification of caspase positive cells in PC3 and DU145 cells treated with ERβ agonist (solid bars) or vehicle control (open bars). (*G*) Quantification of apoptosis (%) in human PCa xenografts from three patients (P1, P2, and P3), treated with vehicle (Con; open bars), castration (Cx; gray bars), or ERβ agonist (ERβ; solid bars). (*H*) Caspase 8 in ERβ-treated PCa; inset negative control. Values are mean ± SEM; $n = 4$ replicates per group except in G, where $n = 3$. nd, not detectable. Analyses by Student's *t* test (*A*, *E*, and *F*) or ANOVA (*B* and *G*). *$P < 0.05$ vs. control; ***$P < 0.005$ vs. control. (Scale bar, *C*, *D*, *H*, and *I*, 25 μm; *F*, 100 μm; and *G*, 200 μm.)

ulations of cells are enriched respectively for stem/progenitor cells (reported to regenerate prostatic acini in vivo) or transit amplifying cells (24–26). To study the in vitro effects of ERβ agonist on these subpopulations, each fraction was replated and treated for 24 h. In unsorted BPH-1 cells, ERβ agonist increased apoptosis 3-fold compared with vehicle controls (Fig. 4*E*). Both CD133$^+$ (putative stem/progenitor) and CD133$^-$ (transient amplifying) cells showed a significant increase in apoptosis in response to the ERβ agonist, as did the nonadherent α2β1integrin^{lo} subpopulation (luminal cell–enriched), which constituted the bulk of the BPH-1 cell cultures (~93%) (Fig. 4*E*). Collectively, these data demonstrated that ERβ agonist induced prostatic apoptosis in xenografted human BPH specimens and in subpopulations of BPH-1 cells, including those enriched for CD133$^+$ that are implicated in regeneration of the prostate and in the transition of benign to malignant disease (26).

ERβ Agonist Induces Androgen-Independent Apoptosis in Human PCa. The expression of caspase-3, -8 and -9 was examined in androgen-independent (ERα$^-$ and ERβ$^+$, Fig. S5) human PCa cell lines, PC3 and DU145. ERβ agonist treatment significantly increased caspase-3 and -8 but not -9 (Fig. 4*F*), confirming use of the extrinsic pathway of apoptosis. Confirmation of the specific induction of apoptosis by ERβ agonist was obtained by siRNA knockdown of ERβ in DU145 cells. The relative efficacy of siRNA against ERβ, negative control siRNA, and transfection control was determined by RT-PCR and showed a >90% reduction of ERβ transcripts in ERβ siRNA–transfected cells. Subsequent treatment of these transfected cells demonstrated that ERβ agonist–induced apoptosis is abrogated in ERβ siRNA–transfected cells (Fig. S7*B*).

To demonstrate an ERβ-induced biological outcome, we s.c. grafted human fluorescent PC3 cells into immuno-deficient host male mice. Tumors were monitored using in vivo fluorescent imaging pre- and posttreatment with vehicle or ERβ agonist. Fluorescent intensity was used as a measure of tumor growth. Our data show a ~2-fold increase in tumor doubling time after ERβ agonist treatment, concurrent with a significant increase in apoptosis and a significant reduction in proliferation, as shown in Table S3.

Finally, we subrenally grafted tissue specimens from three human PCa patients (Gleason Grade 7, epithelial ERβ+, ERα−, Fig S6) into host male mice. After treatment for 3 days, tumor cell apoptosis (detectable by Apoptag staining) was significantly increased after ERβ agonist compared with controls in two of three PCa patient tissues (P1, P2; Fig. 4*G*), and increased in the third patient (P3), although not significantly. In patient 1 (P1), increased caspase 8 immunoreactivity was detected (Fig. 4*H*); further semiquantification of the percent sections expressing caspase 8 showed a 2-fold increase compared with castrate and control tissues. Overall, the data showed ERβ agonist-induced apoptosis in primary PCa xenografts and in androgen-independent PCa cell lines, consistent with the androgen-independent mechanism of action identified in mice.

To confirm that TNFα mediates ERβ-agonist induced apoptosis, we used immunohistochemistry to show that TNFα protein expression was up-regulated in human cell lines and tissues after agonist treatment (Fig. S7*A*). We also used siRNA knockdown of TNFα, reducing TNFα transcripts by ~30%, and showed abrogation of the ERβ-agonist induced apoptotic response in DU145 cells (Fig. S7*C*). Therefore, as shown in animal studies, TNFα mediates ERβ-agonist induced apoptosis in human cells and tissues.

Discussion

This study reports beneficial, proapoptotic actions of selective activation of ERβ without the necessity for androgen withdrawal, in both BPH and PCa, diseases that often occur concurrently in different prostatic zones of aging men. ERβ agonist-induced apoptosis was androgen independent and mediated by TNFα signaling, and thus was mechanistically different from castration (or the effects of ERα agonist). Cellular targets of ERβ agonist were luminal, basal, and stromal cells of BPH tissue and cells, as well as androgen-independent PCa cells lines. Therefore our study unequivocally endorses a proposed anti-proliferative/proapoptotic role for ERβ (13), and provides insight into its mechanism of action and cellular targets. As current therapies for benign and malignant prostate disease (androgen blockade) fail to target castrate-resistant cells and are associated with adverse side effects, these findings imply that ERβ agonists may have significant therapeutic potential for treatment of BPH and/or PCa subject to satisfactory pharmacokinetic and toxicity testing (27, 28).

There are several key differences between the mechanism of apoptosis induced by ERβ agonist and castration that may offer

- This study reports beneficial, pro-apoptotic actions of selective activation of ERβ without the necessity for androgen withdrawal, in both BPH and PCa.
- ERβ agonists may have significant therapeutic potential for treatment of BPH and/or PCa.

some therapeutic advantage. First, ERβ agonist-induced apoptosis via activation of caspase-8 that is not required for castration-induced apoptosis (29) and was absent in TNFαKO mice. The mechanisms of interaction between ERβ and TNFα are unknown; however, we show caspase-8 and -3 activation, and the abrogation of the ERβ-mediated apoptotic response following siRNA knockdown of TNFα in a human prostate cancer cell line. These findings concur with similar data in human hepatocellular carcinoma cell lines where ERβ-activated apoptosis was also mediated by caspase-8 and TNFα (30).

Second, ERβ agonist-induced apoptosis occurs in both the androgen-replete and androgen-deplete milieu. Our conclusion that ERβ agonist action is androgen independent and differs from castration derives from several lines of evidence. In ArKO mice and in human xenografts in which androgen levels are maintained by exogenous testosterone supplementation, or in castrate, androgen-deplete animals, ERβ agonist causes apoptosis, notably in the castrate-resistant androgen-independent basal cell layer. These data concur with our previous report that ERβ is antiproliferative and occurs in tissue recombinants that exclude a role of systemic hormones (21). In addition, ERβ agonist induced apoptosis in androgen-independent DU145 and PC3 PCa cell lines and BPH-1 cells. Thus ERβ agonist may provide an added therapeutic advantage by obviating the side effects of castration or androgen ablation, including hypogonadism, gynecomastia, anemia, and metabolic syndrome in men.

Another key difference between ERβ-induced apoptosis and castration are the cellular targets, as ERβ agonist causes apoptosis in castrate-resistant epithelial cell subpopulations. The main effect of androgen withdrawal is on the terminally differentiated luminal cells that constitute ~95% of the epithelium; yet the basal cell layer, which contains stem/progenitor cells, are resistant to androgen blockade, while expressing high levels of ERβ (31, 32). Although the rate of ERβ-induced apoptosis is low, it is comparable to castration over 3 days (proved to be therapeutically effective); but, different from castration, ERβ targets a subpopulation of epithelial cells, including basal cells that are castrate resistant. It could be argued that this difference is more biologically significant because stem cells within the basal layer are required for normal prostatic regeneration that occurs after repeated cycles of androgen withdrawal and replacement. We showed that, unlike castration, ERβ agonist depletes $p63^+$ prostatic basal cells and perturbs epithelial regeneration following recovery. To further address whether ERβ agonist could affect the putative human prostatic stem cells, we studied a subpopulation (~0.5%) of $CD133^+$ BPH-1 epithelial cells. CD133+ is one of the unique cell surface markers used to enrich for human putative stem cells with demonstrated functional regenerative capacity (25, 26); it is also used to enrich for mouse prostatic stem cells in combination with other markers (33). Here we showed that ERβ induced apoptosis in an enriched $CD133^+$ subpopulation (as well as other cell populations) of BPH-1 cells that are androgen-independent.

In human PCa, castration causes apoptosis in the bulk of tumor cells, but the remaining androgen-independent cells are implicated in disease recurrence. Unlike castration, we show ERβ increased apoptosis in androgen-independent PCa cells (PC3 and DU145), as well as xenografts of primary PCa specimens, expressing ERβ. Whether ERβ agonist targets the castrate-resistant PCa tumor–initiating cells remains to be investigated, and awaits delineation of markers that can isolate and distinguish between normal stem cells and cancer stem cells (25, 26, 34).

Like castration, ERβ targets and induces apoptosis in prostatic stromal cells that play a critical role in the initiation and progression of BPH (and PCa). There are two advantages of ERβ agonist targeting the stroma: first, it has a direct effect on the stromal nodules of BPH themselves; and second, it disrupts stromal–epithelial interactions that are necessary for prostatic epithelial cell proliferation and differentiation (35). Targeting the stroma breaks this cycle of aberrant cell–cell signaling, and therefore it is significant that ERβ agonist targets both stroma as well as epithelial cells, exemplifying its potential therapeutic use. Collectively, the cellular targets of ERβ agonist and castration overlap (including luminal and stromal cells). Uniquely, however, ERβ agonist induces apoptosis in prostatic basal cells, including subpopulations of basal cells enriched for stem/progenitor cells ($\alpha2\beta1^{hi}/CD133^+$), and androgen-independent PCa cells; this is achieved without altering steroid hormone levels.

Overall, this study demonstrates beneficial effects of ERβ agonist on both BPH and PCa cells and human clinical specimens that are mechanistically different from castration, and targets both castrate-responsive and castrate-resistant cells. These studies support the rationale for the preclinical testing and evaluation of the potential for clinical application of estrogen-based therapies, specifically including ERβ agonists, either alone or in combination with existing androgen blockade, for the treatment of BPH and/or PCa. Future replicate studies using other ER agonists are warranted to determine the full potential of this class of agonist.

Materials and Methods

Animals. ArKO or homozygous TNFαKO mice generated by targeted disruption of *cyp19* or *TNFα*, respectively (36, 37), and Balb-c/Nude mice housed at Monash Medical Centre were used at 10–14 weeks of age. NOD/SCID mice were housed at British Columbia (BC) Cancer Research Centre.

Specific ER Modulators. The ERβ-specific agonist (8β-VE2) and ERα-specific agonist (16α-LE_2) were gifted by Drs. Karl-Heinrich Fritzemeier and Katja Prelle (Bayer-Schering Pharma AG). Animals were treated for 3 days by s.c. injection (ERβ [300 μg/kg/d] or ERα agonist [3 μg/kg/d], equivalent volume of peanut oil control) or castration as previously described (21). Testosterone replacement (1-cm Silastic implants of testosterone; Sigma) were given either at the time of initial treatment (3 day experiments) or after treatment (recovery experiments) (additional information on siRNA knockdown of ERβ agonist action in *SI Text*).

Cell Culture Experiments. Human prostate cell lines DU145, PC3, BPH-1, and RWPE-1 were cultured as previously described (38). Cells were treated as follows; cells were plated (2×10^4 cells/well) in multichambered slides (Nalge Nunc International) in low-serum media (5% FCS) for 12 h before being treated with ERβ (6 μM)or vehicle at doses equivalent to those used in mice. After 12 h of treatment, cells were fixed in 10% neutral buffered formalin for immunostaining. Further information on enrichment for CD133+ stem/progenitor cells is given in *SI Text*.

Prostate Tissues and Xenografting. Fresh tissues were processed and implanted in male NOD/SCID mice as previously described (39). Mice received supplementation with testosterone for a period of 2–4 weeks and were divided into three groups: Control (intact mice treated with vehicle); Castrated (castrated mice with no testosterone); and ERβ (intact mice treated for 3 days with ERβ, 300 μg/kg/d). Additionaldetails on patient selection and sample selection are given in *SI Text*.

Immunohistochemistry. Immunohistochemical staining was performed as previously described (21). Antibodies used were as follows: high-molecular-weight cytokeratins (CKH), PCNA, ERα (DAKO), androgen receptor (*AR*); p63 (Santa Cruz Biotechnology) and ERβ (Novocastra Laboratories Ltd) using previously described protocols (21). Apoptosis was detected using ApopTag Plus Peroxidase In situ Apoptosis detection kit (Chemicon) or with antibodies to cleaved caspase-3, -8, -9 according to the instructions of the manufacturer (Cell Signaling Technology). Details on dual immunofluorescence and quantification of immunostaining are provided in *SI Text*.

RNA Extraction and Oligo Gene Expression Array. Total RNA was extracted from prostate tissues using TRIzol reagent (Invitrogen Life Technologies) as previously described (38). Gene expression analysis was conducted using GEArray DNA microarray (OMM-012; SuperArray Bioscience Corp.) Details are provided in *SI Text*.

Statistical Analysis. Data were analyzed to determine normality, and significant differences were determined by either *t* test or one-way ANOVA (Prism 5.00, GraphPad Software Inc.) followed by Tukey posthoc analyses. Significance was accepted at $P < 0.05$. Data are expressed as mean ± SEM unless otherwise noted.

- ERβ targets and induces apoptosis in prostatic stromal cells that play a critical role in the initiation and progression of BPH and PCa.
- ERβ agonist targets both stroma as well as epithelial cells, exemplifying its potential therapeutic use.
- Uniquely, however, ERβ agonist induces apoptosis in prostatic basal cells; this is achieved without altering steroid hormone levels.
- These studies support potential for clinical application of estrogen-based therapies.

Aromatase Inhibition Reduces Insulin Sensitivity in Healthy Men

Aromatase Inhibition Reduces Insulin Sensitivity in Healthy Men

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Context: Deficiency of aromatase, the enzyme which catalyzes the conversion of androgens to estrogens, is associated with insulin resistance in humans and mice.

Objective: We hypothesized that pharmacological aromatase inhibition results in peripheral insulin resistance in humans.

Design: Double-blind randomized controlled crossover study.

Setting: A clinical research facility.

Participants: 17 healthy male volunteers (18 – 50 years).

Intervention: Oral anastrozole (1mg daily) and placebo, each for 6 weeks with 2 week 'washout' period.

Main outcome measure: Glucose disposal and rates of lipolysis were measured during a stepwise hyperinsulinemic euglycemic clamp. Data are mean (SEM).

Results: Anastrozole therapy resulted in significant estradiol suppression (59.9 ± 3.6 vs. 102.0 ± 5.7 pmol/L, P = <0.001) and more modest elevation of total testosterone (25.8 ± 1.2 vs. 21.4 ± 0.7 nmol/L, P = 0.003). Glucose infusion rate, during low dose insulin infusion, was lower following anastrozole administration (12.16 ± 1.33 vs. 14.15 ± 1.55 μmol/kg/min, P = 0.024). No differences in hepatic glucose production or rate of lipolysis were observed.

Conclusion: Aromatase inhibition reduces insulin sensitivity, with respect to peripheral glucose disposal, in healthy men. Local generation and action of estradiol, at the level of skeletal muscle, is likely to be an important determinant of insulin sensitivity.

Although best known for their role in reproduction, both androgens and estrogens exert metabolic effects (1). In men, testosterone deficiency is associated with an increased risk of type 2 diabetes mellitus (T2DM) (2) and pharmacological androgen deprivation, employed in the treatment of prostate cancer, is associated with deteriorating insulin sensitivity (3). There is inconsistent evidence that testosterone replacement therapy improves insulin sensitivity in hypogonadal men (4, 5).

In postmenopausal women, estrogen replacement reduces the risk of T2DM (6). Estrogens are generated from substrate androgens through the action of the cytochrome P450 enzyme aromatase (7). The circulating concentration of estrogens may be much less important than local tissue generation, particularly in men and postmenopausal women, in whom the local activity of aromatase in skeletal muscle and adipose tissue is likely to account for most estrogen production and action (8). It is possible that

Abbreviations:

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- CONCLUSION: Aromatase inhibition reduces insulin sensitivity, with respect to peripheral glucose disposal, in healthy men.
- Local action of estradiol, at the level of skeletal muscle, is likely to be an important determinant of insulin sensitivity.

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earlier observations in aromatase knockout mice (30), albeit the number of paired biopsies we obtained was small and these investigations of secondary endpoints risk being underpowered. Since insulin stimulates skeletal muscle NEFA uptake (31) and estrogen deprivation in mice reduces the capacity for skeletal muscle fat oxidation (32), it is also possible that any change in NEFA suppression reflects effects of aromatase inhibition in skeletal muscle.

No differences were observed in body composition as determined by BMI, weight or body fat percentage between placebo and anastrozole phases. This is not unexpected after only 6 weeks of therapy. 16 weeks of aromatase inhibition therapy in men has been shown to increase body fat, particularly in the intra-abdominal compartment, as assessed by sensitive CT and DEXA analysis (13). Following anastrozole treatment, we observed a 28% reduction in leptin, consistent with the findings of a previous study investigating the effects of letrozole in healthy men (21). Leptin is preferentially secreted by subcutaneous rather than omental adipocytes (33), raising the possibility that the observed difference in leptin may represent a shift from subcutaneous to visceral adipose deposition. There was no effect of anastrozole on subcutaneous adipose leptin mRNA expression, suggesting lower serum leptin concentration is not a consequence of a direct effect upon transcription in the subcutaneous depot. A subtle shift in fat distribution might indirectly contribute to the observed changes in insulin sensitivity.

Aromatase inhibition in postmenopausal women is associated with profound (>90%) suppression of estradiol (34). However this is not the case in men, where a compensatory increase in LH (and substrate androgens) attenuates the degree of estradiol suppression. While the 41.3% decline in estradiol we observed is consistent with previous reports with letrozole (35, 21) (22), the compensatory rise in testosterone was several-fold lower. Letrozole is more abundant than anastrozole in mouse brain tissue following systemic administration (36), providing a potential explanation for the more modest elevation in LH with anastrozole (31.4% compared to 335%) (35). Notably, this is the first investigation of the metabolic effects of aromatase inhibition to utilize LC MS/MS analysis of plasma sex steroid concentrations. The superiority of mass spectrometric analysis has been demonstrated in the context of aromatase inhibition, where immunometric methods are prone to significantly underestimate estradiol suppression in postmenopausal women (34).

Accordingly, this study with anastrozole is less susceptible than previous studies with letrozole to the criticism that metabolic sequelae are attributable to testosterone excess rather than estrogen deficiency, although we cannot exclude an effect related to the modest (mean 4.4 nmol/L) rise in total testosterone. In men and postmenopausal women, local generation and action of estradiol in adipose tissue and skeletal muscle is likely to be more physiologically relevant than distant action. Plasma concentration of estradiol does not necessarily reflect tissue concentration, as evidenced by the similar breast tissue levels observed in pre- and postmenopausal women, despite markedly divergent plasma concentrations (37). In previous aromatase inhibitor studies in men (21) where supraphysiological plasma testosterone concentrations were achieved, the greater delivery of substrate androgens may have limited the desired effect of minimizing local estrogen generation and action in target tissues. It would be desirable to directly assess the effects of aromatase inhibition upon target tissue sex steroid hormone concentration.

Anastrozole resulted in a significant reduction in total cholesterol, in contrast to previous studies, which have shown the opposite effect upon LDL cholesterol in healthy younger men (21) or no effect in older men with mild hypogonadism (27). These conflicting findings may reflect differences in the populations studied as well as the less pronounced elevation in plasma testosterone observed in our study.

The rise in systolic BP and lower heart rate observed during aromatase inhibitor treatment was unexpected and contrasts with lower diastolic BP, elevated heart rate as well as reduced baroreflex sensitivity in aromatase knockout mice (38). Estrogens are likely to exert hemodynamic effects at both a central and peripheral level, potentially in a gender-specific manner, demanding further detailed assessment of the consequences of aromatase inhibition.

In summary, as hypothesized, in healthy men aromatase inhibition resulted in decreased insulin sensitivity, primarily manifest as reduced peripheral glucose disposal. No significant effects upon hepatic glucose production or lipolysis were observed. These results suggest suppression of estrogen action in skeletal muscle is the principal mechanism through which aromatase inhibitors exert a deleterious effect on glucose metabolism. This lends support to the hypothesis that, in male androgen deficiency, insulin resistance is largely a consequence of reduced aromatase substrate availability and consequent local estrogen deficiency in target tissue. The metabolic consequences for patients treated with aromatase inhibitors for breast cancer deserve closer investigation.

Acknowledgments

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- 16 weeks of aromatase inhibition therapy in men has been shown to increase body fat, particularly in the intra-abdominal compartment.
- In summary, as hypothesized, in healthy men aromatase inhibition resulted in decreased insulin sensitivity.
- Suppression of estrogen action in skeletal muscle is the principal mechanism through which aromatase inhibitors exert a deleterious effect on glucose metabolism.

Testosterone Treatment and Sexual Function in Older Men with Low Testosterone Levels

Testosterone Treatment and Sexual Function in Older Men with Low Testosterone Levels

Glenn R. Cunningham, Alisa J. Stephens-Shields, Raymond C. Rosen, Christina Wang, Shalender Bhasin, Alvin M. Matsumoto, J. Kellogg Parsons, Thomas M. Gill, Mark E. Molitch, John T. Farrar, David Cella, Elizabeth Barrett-Connor, Jane A. Cauley, Denise Cifelli, Jill P. Crandall, Kristine E. Ensrud, Laura Gallagher, Bret Zeldow, Cora E. Lewis, Marco Pahor, Ronald S. Swerdloff, Xiaoling Hou, Stephen Anton, Shehzad Basaria, Susan J. Diem, Vafa Tabatabaie, Susan S. Ellenberg, and Peter J. Snyder*

Context: The Testosterone Trials are a coordinated set of seven trials to determine the efficacy of T in symptomatic men ≥65 years old with unequivocally low T levels. Initial results of the Sexual Function Trial showed that T improved sexual activity, sexual desire, and erectile function.

Objective: To assess the responsiveness of specific sexual activities to T treatment; to relate hormone changes to changes in sexual function; and to determine predictive baseline characteristics and T threshold for sexual outcomes.

Design: A placebo-controlled trial.

Setting: Twelve academic medical centers in the United States.

Participants: A total of 470 men ≥65 years of age with low libido, average T <275 ng/dL, and a partner willing to have sexual intercourse at least twice a month.

Methods: Men were assigned to take T gel or placebo for 1 year. Sexual function was assessed by three questionnaires every 3 months: the Psychosexual Daily Questionnaire, the Derogatis Interview for Sexual Function, and the International Index of Erectile Function.

Results: Compared with placebo, T administration significantly improved 10 of 12 measures of sexual activity. Incremental increases in total and free T and estradiol levels were associated with improvements in sexual activity and desire, but not erectile function. No threshold T level was observed for any outcome, and none of the 27 baseline characteristics predicted responsiveness to T.

Conclusions: In older men with low libido and low T levels, improvements in sexual desire and activity in response to T treatment were related to the magnitude of increases in T and estradiol levels, but there was no clear evidence of a threshold effect. (*J Clin Endocrinol Metab* 101: 0000–0000, 2016)

Testosterone treatment improves sexual function in younger men who have T deficiency due to disorders of the testes, the pituitary, or the hypothalamus (1, 2) or to administration of a GnRH agonist (3, 4) or antagonist (5). However, the efficacy of T treatment in improving sexual function in older men with age-related decline of T levels remains unclear (6, 7). Meta-analyses have found that T treatment improves libido and to a lesser degree erectile function in predominantly middle-aged men with low total T levels (8, 9). These analyses were based upon a limited number of trials, several of which included fewer than 60 men and none of which included more than 140 men per treatment arm. T treatment has improved sexual function in some trials, but not in others (6, 10–12). Most

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Abbreviations: BMI, body mass index; DISF-SOD, Derogatis Interview for Sexual Function-Sexual Desire Domain; EFD, Erectile Function Domain; IIEF, International Index of Erectile Function; OFD, Orgasmic Function Domain; PANAS, Positive and Negative Affect Scales; PDE5, phosphodiesterase type 5; PDQ, Psychosexual Daily Questionnaire; PDQ-D4, question 4 of the PDQ.

- T administration significantly improved 10 of 12 measures of sexual activity.
- Incremental increases in total and free T and estradiol levels were associated with improvements in sexual activity and desire.
- No threshold T level was observed for any outcome.
- CONCLUSIONS: Improvements in sexual desire and activity in response to T treatment were related to the magnitude of increases in T and estradiol levels, but there was no clear evidence of a threshold effect.

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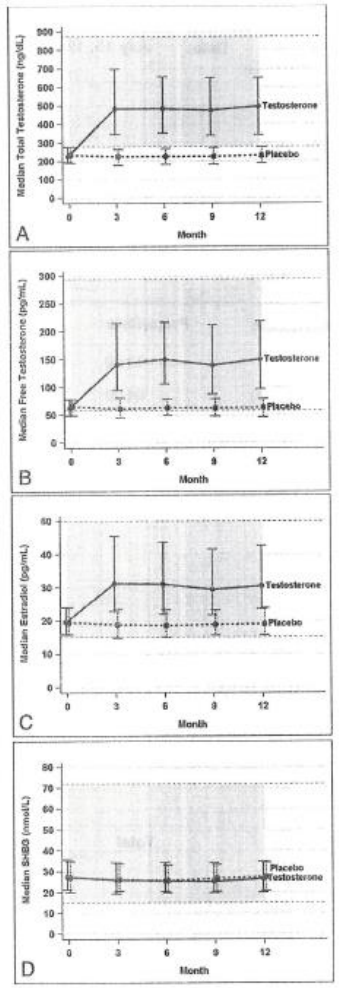

Figure 1. Total (A) and free (B) T, estradiol (C), and SHBG (D) levels at baseline and during treatment.

teristics influenced the effects of T treatment on primary and secondary endpoints in men in the Sexual Function Trial. Of the 27 baseline characteristics tested, only alcohol use appeared to influence the effect of T on sexual activity and sexual desire; more drinks per week were associated with a greater effect of T on sexual desire and activity scores. History of a stroke and higher scores on the International Prostate Symptom Score appeared to reduce the effect of T on sexual desire. Higher scores on the Positive and Negative Affect Scales (PANAS) and a history of coronary artery disease were associated with a lesser effect of T on erectile function. These interactions were all nominally significant at the 0.05 level, but none were significant after adjusting for multiple comparisons (31). Cardiovascular risk scores showed no association with responsiveness to T treatment (data not shown).

Relation of the changes in hormone levels with changes in sexual activity, desire, and erectile function

The magnitude of changes in total and free T and estradiol levels was significantly associated with the magnitude of improvements in sexual activity and sexual desire, but not erectile function (Table 2). Although these increments are small, the changes in the PDQ-Q4 and the DISF-SDD were highly significant. Increments in estradiol levels, but not in total or free T, were associated with greater improvement in orgasmic function. The IIEF-OFD score appears more strongly related to changes in estradiol levels than to changes in other hormones. We also compared changes in the DISF-SDD, PDQ-Q4, and IIEF-EFD for men with and without diabetes. In men assigned to T, there were no significant differences between persons with diabetes and nondiabetics for PDQ-Q4, DISF-SDD, or IIEF-EFD. In the placebo arm, a change in IIEF-EFD was on average 1.4 points higher in nondiabetic men than diabetic men ($P = .04$), but this difference is not expected to be clinically relevant. There were no significant differences in responses to the PDQ-Q4 or DISF-SDD in men treated with placebo. Our threshold analyses did not reveal any thresholds of sex steroid values with any of the sexual function outcomes (data not shown).

Discussion

To date, the Sexual Function Trial of the TTrials is the largest placebo-controlled trial of the efficacy of T on sexual function in older men with low libido and unequivocally low T levels. T administration was associated with consistent improvements in 10 of the 12 measures of sexual interests and activities, as assessed by PDQ-Q4. These include frequency of intercourse, masturbation, and nocturnal erections. Only "flirting by others" and "day spontaneous erections" were not changed by T treatment. Sexual desire and activity increased with increases in cir-

- The magnitude of changes in total and free T and estradiol levels was significantly associated with the magnitude of improvements in sexual activity and sexual desire.
- Increments in estradiol levels, but not in total or free T, were associated with greater improvement in orgasmic function.

The TTrials have many strengths and some limitations. The TTrials required two low, early morning, fasting total T levels in men ≥65 years of age who did not have an organic cause for hypogonadism. The Sexual Function Trial also required low libido. We also used state-of-the-art hormone assays. The trial was powered at 90%, placebo-controlled, and double-blinded. We monitored total T levels and made dose adjustments to achieve and maintain serum T levels in the target range, while maintaining blinding. Finally, we used validated instruments to assess outcomes. Our primary outcome, sexual activity, utilized the PDQ-Q4, which had been shown to be responsive to T treatment in previous T trials (27, 30).

The men in the Sexual Function Trial were required to be in a stable relationship with a partner; however, we did not assess or control for partner sexual function or other partner factors, which may have influenced the results. T treatment increases estradiol levels as well as T levels, but the study design did not allow us to determine whether estradiol has an independent effect on sexual function.

In summary, T treatment of older men with low T levels consistently improved most types of sexual activity, sexual desire, and erectile function in older men with low libido and low T levels. The improvements in sexual desire, sexual interests, and sexual activities were related to changes in T, free T, and estradiol levels. We found no clinical characteristics that predicted responsiveness to T treatment and no T threshold for improving sexual function.

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The investigators developed the protocol with assistance from the National Institutes of Health. AbbVie did not participate in the design, conduct of the trials, analysis, or reporting of the data. All authors participated in the design and conduct of the trials. Trial statisticians performed all data analyses. The first author wrote the first draft of the manuscript, and all authors contributed to subsequent drafts.

Clinical Trials.gov number: NCT00799617.

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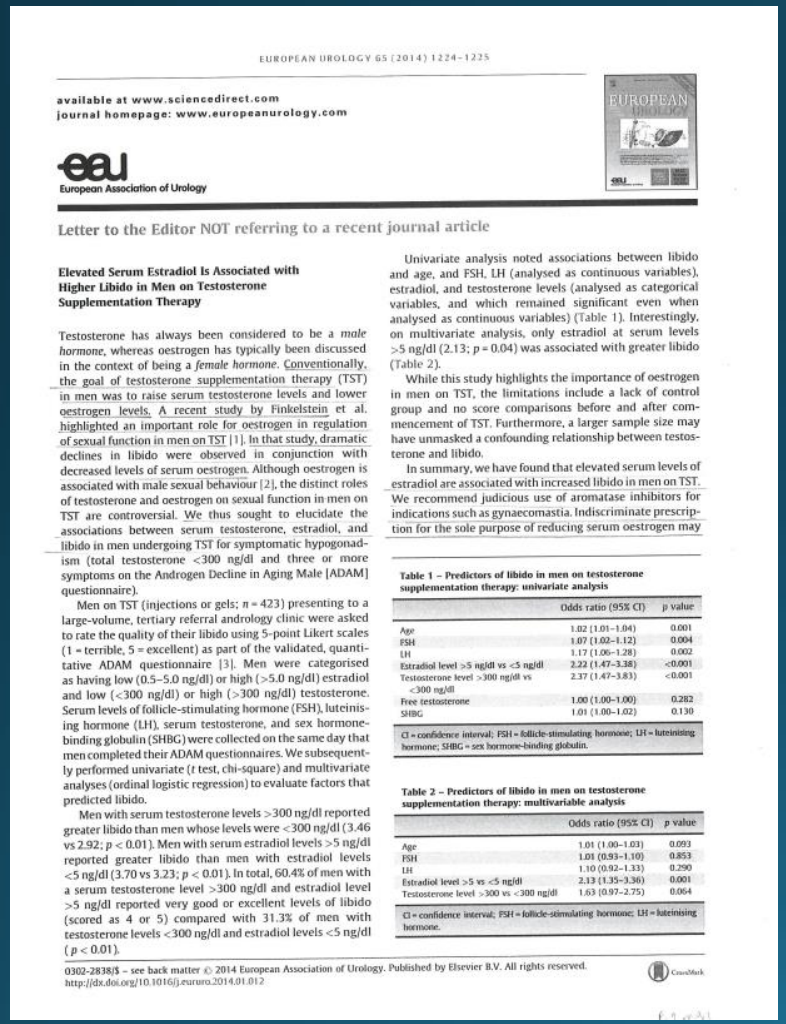
- In summary, T treatment of older men with low T levels consistently improved most types of sexual activity, sexual desire, and erectile function in older men with low libido.
- The improvements in sexual desire, sexual interests, and sexual activities were related to changes in T, free T, and estradiol levels.

Elevated Serum Estradiol is Associated with Higher Libido in Men on Testosterone Supplementation Therapy



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Letter to the Editor NOT referring to a recent journal article

Elevated Serum Estradiol Is Associated with Higher Libido in Men on Testosterone Supplementation Therapy

Testosterone has always been considered to be a *male hormone*, whereas oestrogen has typically been discussed in the context of being a *female hormone*. Conventionally, the goal of testosterone supplementation therapy (TST) in men was to raise serum testosterone levels and lower oestrogen levels. A recent study by Finkelstein et al. highlighted an important role for oestrogen in regulation of sexual function in men on TST [1]. In that study, dramatic declines in libido were observed in conjunction with decreased levels of serum oestrogen. Although oestrogen is associated with male sexual behaviour [2], the distinct roles of testosterone and oestrogen on sexual function in men on TST are controversial. We thus sought to elucidate the associations between serum testosterone, estradiol, and libido in men undergoing TST for symptomatic hypogonadism (total testosterone <300 ng/dl and three or more symptoms on the Androgen Decline in Aging Male [ADAM] questionnaire).

Men on TST (injections or gels; $n = 423$) presenting to a large-volume, tertiary referral andrology clinic were asked to rate the quality of their libido using 5-point Likert scales (1 = terrible, 5 = excellent) as part of the validated, quantitative ADAM questionnaire [3]. Men were categorised as having low (0.5–5.0 ng/dl) or high (>5.0 ng/dl) estradiol and low (<300 ng/dl) or high (>300 ng/dl) testosterone. Serum levels of follicle-stimulating hormone (FSH), luteinising hormone (LH), serum testosterone, and sex hormone-binding globulin (SHBG) were collected on the same day that men completed their ADAM questionnaires. We subsequently performed univariate (*t* test, chi-square) and multivariate analyses (ordinal logistic regression) to evaluate factors that predicted libido.

Men with serum testosterone levels >300 ng/dl reported greater libido than men whose levels were <300 ng/dl (3.46 vs 2.92; $p < 0.01$). Men with serum estradiol levels >5 ng/dl reported greater libido than men with estradiol levels <5 ng/dl (3.70 vs 3.23; $p < 0.01$). In total, 60.4% of men with a serum testosterone level >300 ng/dl and estradiol level >5 ng/dl reported very good or excellent levels of libido (scored as 4 or 5) compared with 31.3% of men with testosterone levels <300 ng/dl and estradiol levels <5 ng/dl ($p < 0.01$).

Univariate analysis noted associations between libido and age, and FSH, LH (analysed as continuous variables), estradiol, and testosterone levels (analysed as categorical variables, and which remained significant even when analysed as continuous variables) (Table 1). Interestingly, on multivariate analysis, only estradiol at serum levels >5 ng/dl (2.13; $p = 0.04$) was associated with greater libido (Table 2).

While this study highlights the importance of oestrogen in men on TST, the limitations include a lack of control group and no score comparisons before and after commencement of TST. Furthermore, a larger sample size may have unmasked a confounding relationship between testosterone and libido.

In summary, we have found that elevated serum levels of estradiol are associated with increased libido in men on TST. We recommend judicious use of aromatase inhibitors for indications such as gynaecomastia. Indiscriminate prescription for the sole purpose of reducing serum oestrogen may

Table 1 – Predictors of libido in men on testosterone supplementation therapy: univariate analysis

	Odds ratio (95% CI)	p value
Age	1.02 (1.01–1.04)	0.001
FSH	1.07 (1.02–1.12)	0.004
LH	1.17 (1.06–1.28)	0.002
Estradiol level >5 ng/dl vs <5 ng/dl	2.22 (1.47–3.38)	<0.001
Testosterone level >300 ng/dl vs <300 ng/dl	2.37 (1.47–3.83)	<0.001
Free testosterone	1.00 (1.00–1.00)	0.282
SHBG	1.01 (1.00–1.02)	0.130

CI = confidence interval; FSH = follicle-stimulating hormone; LH = luteinising hormone; SHBG = sex hormone-binding globulin.

Table 2 – Predictors of libido in men on testosterone supplementation therapy: multivariable analysis

	Odds ratio (95% CI)	p value
Age	1.01 (1.00–1.03)	0.093
FSH	1.01 (0.93–1.10)	0.853
LH	1.10 (0.92–1.33)	0.290
Estradiol level >5 vs <5 ng/dl	2.13 (1.35–3.36)	0.001
Testosterone level >300 vs <300 ng/dl	1.63 (0.97–2.75)	0.064

CI = confidence interval; FSH = follicle-stimulating hormone; LH = luteinising hormone.

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- Conventionally, the goal of testosterone supplementation therapy in men was to raise serum testosterone levels and lower oestrogen levels.
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- In that study, dramatic declines in libidio were observed in conjunction with decreased levels of serum oestrogen.

- We thus sought to elucidate the associations between serum testosterone, estradiol, and libido in men undergoing TST.
- We have found that elevated serum levels of estradiol are associated with increased libido in men on TST.
- We recommend judicious use of aromatase inhibitors for indications such as gynaecomastia. Indiscriminate prescription for the sole purpose of reducing serum oestrogen may be met with poor libido, decreasing satisfaction and quality of life.

High Estrogen in Men After Injectable Testosterone Therapy: The Low T Experience

Article

High Estrogen in Men After Injectable Testosterone Therapy: The Low T Experience

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Abstract

Testosterone replacement improves quality of life and is aromatized in men in adipose tissues to estrogen. Hyperestrogenism is believed to be harmful to male sexuality. This is a description of our experience of screening 34,016 men in the Low T Centers, of which approximately 50% were converted to treatment. Men were treated with injectable testosterone, and we have available data from 2009 to 2014. The data were extracted from our electronic health record (AdvancedMD) of 35 Low T Centers across the United States. In all, 7,215 (20.2%) out of the 34,016 patients had high estradiol levels defined as ≥42.6 pg/ml. Estradiol was measured using electro-chemiluminescence immunoassay. Of the patients who had high estradiol levels, the age distribution was as follows: 132/989 (13.3%) were older than 65 years, 3,753/16,955 (22.1%) were between 45 and 65 years; 2,968/15,857 (18.7%) were between 25 and 44 years, 7/215 (3.3%) were younger than 25 years. The difference between extreme age groups (<25 and ≥65) was statistically significant using a chi-square test ($p = .013$). The correlation coefficient of serum estradiol to age was .53, $SD = 8.21$. It was observed that practitioners used aromatase inhibitor and selective estrogen receptor modulator to treat symptoms of hyperestrogenism, irrespective of blood estradiol levels. Gynecomastia was rarely documented as a reason for the prescription. Our finding was that high estradiol levels were not associated with higher rates of low libido but established higher rates of documented low libido with those with normal or lower estradiol levels. The difference was statistically significant ($p < .05$).

Keywords

testosterone therapy, estrogen, age, aromatase inhibitor/SERM, gynecomastia

Introduction

Testosterone is a hormone that is synthesized from cholesterol and is broken down to various metabolites, including 17 beta-estradiol (E2) and 5 alpha-dihydrotestosterone (DHT). E2 is derived from aromatization of testosterone in adipose tissues, whereas dihydrotestosterone is derived from 5 alpha reduction of testosterone. In our practices, it was observed that patients develop tender nipples from gynecomastia after injectable testosterone therapy. This could be the result of increased testosterone levels after treatment, which in turn aromatizes into E2. The development of breast tissue in men appears to be directly linked to rises in testosterone levels, E2 levels, and obesity. The Low T Centers have had 4 years experience treating large populations of hypogonadal patients and thus sought to understand if there were predictive factors of patients who were more likely to develop high estradiol levels after treatment with testosterone. We wanted to examine specifically the influence of age and whether there was an impact on the aromatization of testosterone to E2. The aging process is often associated with weight gain, particularly in the middle age groups (Dahl, Reynolds, Fall, Magnusson, & Pedersen, 2013). A physiological change also occurs with aging, as the body exchanges lean body mass for fat. This has a direct influence on drug pharmacokinetics and pharmacodynamics. For example, with aging the higher fat content can influence fat soluble drugs by increasing their half lives and

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- It was observed that practitioners used an aromatase inhibitor to treat symptoms of hyperestrogenism, irrespective of blood estradiol levels.
- Gynecomastia was rarely documented as a reason for the prescription.
- Our finding was that high estradiol levels were not associated with low libido.
- However, there were higher rates of low libido in those with normal or lower estradiol levels.

although 34,016 patients who presented to the Centers were screened, only 50% were eligible for treatment, based on inclusion and exclusion factors. The analysis was done on patients who presented to the Centers and were screened and not limited to those on treatment. The correlation of libido is definitely an area for further study.

The effects of estradiol on the human brain are unclear. Currently, there are no hormone markers within the brain to determine the association of levels of sex hormones with libido. In this study a presumption was made that serum estradiol reflects brain estradiol levels or activity. It may be possible that if serum estradiol level is low more estradiol is available for the brain, as it is shifted from the rest of the body to the brain. This hypothesis is given to support the results of our study, of not associating low libido to higher estradiol levels. In a previous study, positive emission tomography was used in an attempt to map areas of the brain involved in glucose metabolism after administration of testosterone. The brain stem and parietal lobes were highly metabolic, suggesting that these areas are involved in sexual processing (Tan, 2013). There are current arguments for an optimal T:E2 ratio for sexuality (Shabsigh et al., 2005), rather than the actual amounts, but studies are weakly powered.

Conclusion

Not much work has been done to understand better the role of estrogens in men. There has also been a distinction between work done on endogenous estrogens and also exogenous estrogens, be it given as estrogen itself or converted from testosterone. Our work in a large database of 34,016 patients represents one of the first attempts to understand the characteristics of exogenous estrogens, which in this case are aromatized from exogenous testosterone given to treat hypogonadism. From our study, it appears that age may be a determinant of the conversion of testosterone to estrogens, except for later years in life after 65 years. The clinical importance of high estrogen after TRT continues to be debated. In our study, high estrogen after TRT does not necessarily associate with low libido. However, AI and SERM were prescribed frequently (30% of cases). There are challenges in setting up a guideline for the threshold beyond which AI and SERM are to be used, as there are no evidence-based studies at this time to guide the practice. Normality based on standard deviation can be used, but our study reports that age in itself may cause variations in normal values. Although our study did not associate low libido with high E2 levels; there may be foreseeable dangers to exposure to high estrogen over a longer period of time (Lerchbaum et al., 2011). The use of AI and SERM should be individualized and carefully monitored. The common side effects of AIs include constipation, diarrhea, nausea, vomiting, upset stomach, loss of appetite, body aches and pains, breast swelling/tenderness/pain, headache, dry mouth, scratchy throat, increased cough, dizziness, trouble sleeping, tiredness/weakness, flushing and sweating (hot flashes/hot flushes), hair thinning, and weight change and should be communicated to the patent. Changes in diet such as eating several small meals may help lessen the chance of nausea and vomiting. More work such as a longitudinal, controlled study is needed to assess the role of exogenous estrogens from TRT and the need to treat this condition.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Opal Medical Clinic is not related to Low T Centers. Mr. Cook and Dr. Reilly see patients at the Low T Centers but are neither employees nor shareholders and are independent contractors.

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Gooren, L. J. (1985). Human male sexual functions do not require aromatization of testosterone: A study using

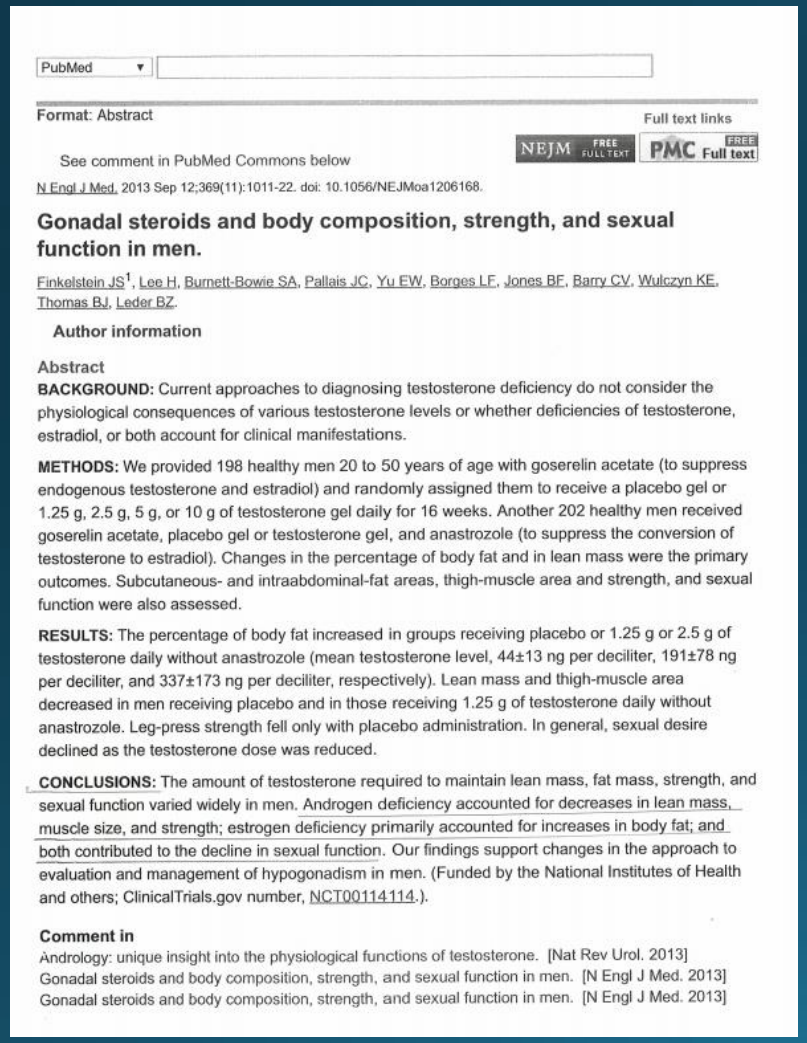
Conclusion:

The common side effects of AIs included-

- Body aches and pains
- Breast swelling/tenderness/pain
- Headache
- Trouble sleeping
- Tiredness/weakness
- Flushing and sweating
- Hair thinning
- Weight changes

These side effects should be communicated to the patient.

Gonadal steroids and body composition, strength, and sexual function in men



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Gonadal steroids and body composition, strength, and sexual function in men.

Finkelstein JS[1], Lee H, Burnett-Bowie SA, Pallais JC, Yu EW, Borges LF, Jones BF, Barry CV, Wulczyn KE, Thomas BJ, Leder BZ.

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Abstract

BACKGROUND: Current approaches to diagnosing testosterone deficiency do not consider the physiological consequences of various testosterone levels or whether deficiencies of testosterone, estradiol, or both account for clinical manifestations.

METHODS: We provided 198 healthy men 20 to 50 years of age with goserelin acetate (to suppress endogenous testosterone and estradiol) and randomly assigned them to receive a placebo gel or 1.25 g, 2.5 g, 5 g, or 10 g of testosterone gel daily for 16 weeks. Another 202 healthy men received goserelin acetate, placebo gel or testosterone gel, and anastrozole (to suppress the conversion of testosterone to estradiol). Changes in the percentage of body fat and in lean mass were the primary outcomes. Subcutaneous- and intraabdominal-fat areas, thigh-muscle area and strength, and sexual function were also assessed.

RESULTS: The percentage of body fat increased in groups receiving placebo or 1.25 g or 2.5 g of testosterone daily without anastrozole (mean testosterone level, 44±13 ng per deciliter, 191±78 ng per deciliter, and 337±173 ng per deciliter, respectively). Lean mass and thigh-muscle area decreased in men receiving placebo and in those receiving 1.25 g of testosterone daily without anastrozole. Leg-press strength fell only with placebo administration. In general, sexual desire declined as the testosterone dose was reduced.

CONCLUSIONS: The amount of testosterone required to maintain lean mass, fat mass, strength, and sexual function varied widely in men. Androgen deficiency accounted for decreases in lean mass, muscle size, and strength; estrogen deficiency primarily accounted for increases in body fat; and both contributed to the decline in sexual function. Our findings support changes in the approach to evaluation and management of hypogonadism in men. (Funded by the National Institutes of Health and others; ClinicalTrials.gov number, NCT00114114.).

Comment in

Andrology: unique insight into the physiological functions of testosterone. [Nat Rev Urol. 2013]
Gonadal steroids and body composition, strength, and sexual function in men. [N Engl J Med. 2013]
Gonadal steroids and body composition, strength, and sexual function in men. [N Engl J Med. 2013]

- Androgen deficiency accounted for decreases in lean mass, muscle size, and strength.
- Estrogen deficiency primarily accounted for increases in body fat.
- Both contributed to the decline in sexual function.

SUMMARY

- After 50 years of administering IM testosterone to men which significantly raises estrogen levels, what study showed harm of raising estradiol levels and what study showed benefit to lowering estradiol levels in men?
- All studies show benefit to raising estradiol with T.
- All studies show benefit in giving E2 to men.
- No intervention study showed harm in raising E2 levels.
- All studies show harm by blocking estradiol with aromatase inhibitors.

Points to Ponder:

- If estrogen causes prostate cancer, then why don't the urologists prescribe AI to protect the prostate?
- If estrogen increases the risk of heart disease in men, then why don't we see it in any study of testosterone administration?
- If estrogen causes prostate cancer, and giving testosterone to men increases estrogen levels, then why is there no study in the last 50 years (of which there are several hundred) that shows an increase incidence of prostate cancer?
- If estrogen increases prostate cancer, then why are there multiple studies that prove estrogen treats prostate cancer?
- If estrogen is harmful in men, then why are there no studies that show increasing estrogen, or giving estrogen, show any harm?
- If estrogen is harmful to men, then why are there no studies showing that aromatase inhibitors are of any benefit?
- If estrogen is harmful to men, then why do all the studies using aromatase inhibitors in men show harm and no benefit?

Thank you,
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