The Role and Management of Estradiol in Men: Data Review

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This information is not a recommendation nor is it intended to provide direction regarding diagnoses, treatments, or potential outcomes.

Any interpretation of this information should be used by the prescriber at his/her discretion.

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For the handout of the entire presentation (135 slides), visit this link

bit.do/estradiolmen

For a free download of Nelson's Book "Testosterone: A Man's Guide" and other offers, visit this link

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Hormone Stigma & “Bad” Hormones

- “Women don’t have or need testosterone”
- “Men’s should knock down their estradiol”
- “Testosterone will make you aggressive.”
- “Estradiol will make a man moody, bloated and asexual, and make him grow boobs”

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Agenda

- Limitations of current data
- Blood test accuracy
- Estradiol in Men 101 (roles, estrogen types, epidemiology)
- Review of studies:
    - Is there any evidence of potential effects of high/low estradiol blood levels?:
        - HIGH
            - Water retention.
            - Nipple sensitivity.
            - Mood changes
            - Gynecomastia
            - Erectile dysfunction (venous leakage)
            - Increased fat mass
            - Prostate cancer
        - LOW:
            - Bone loss
            - Increased fat mass (viscous cycle)
            - Decreased Libido
            - Joint pain
            - Worsening of lipids/cardiovascular disease
            - Cognitive dysfunction?
- Should we monitor T/E2 ratio ?
- Is there a sweet spot?
- What is not covered today can be accessed for free on ClinicOptimizers.com by end of Feb 2017. (Appendices 1-7)

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Limitations of Current Data

- Most data comes from men with total testosterone under 350 nd/dl
- Most studies used old E2 (Immunoassay) test instead of the LC/MS based one (sensitive E2)
- No upper QOL-related limits have been studied in men on TRT.
- Lower limit is becoming clear (10-15 pg/mL) to prevent bone loss, fat gain and decreased sexual function.
- Only 3 studies explored T/E2 ratios
- Only 2 contradictory studies (epileptic men) using anastrozole in men on TRT at 1 mg/day to improve libido.

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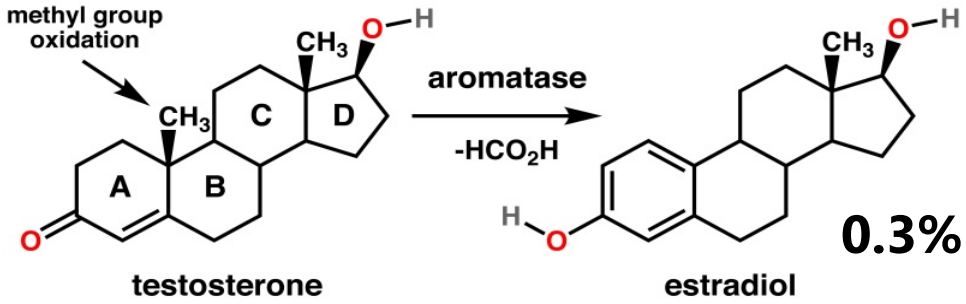
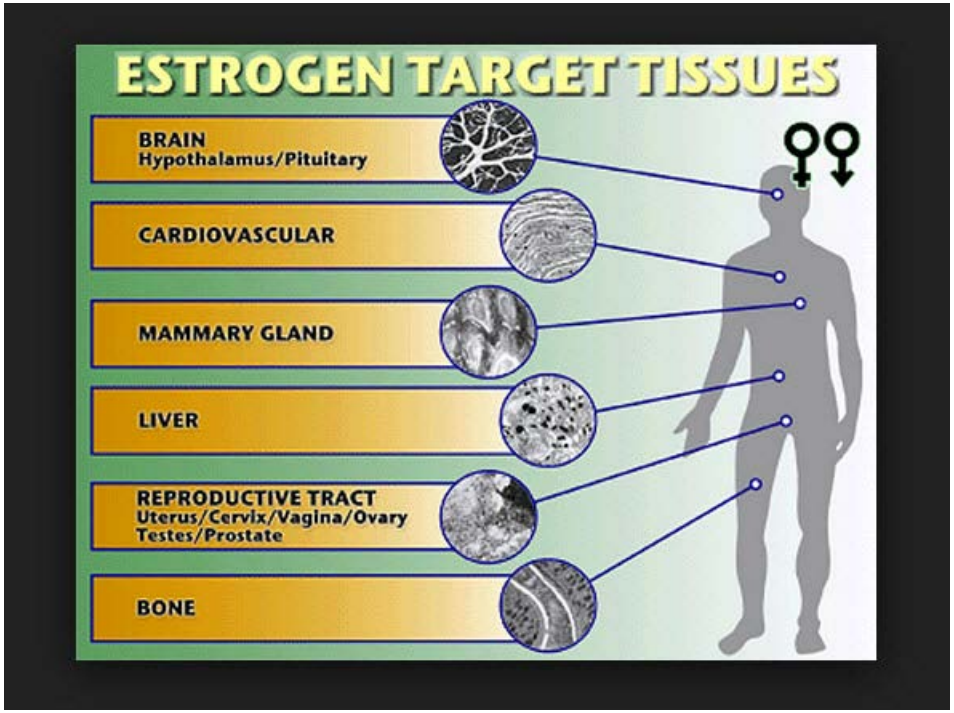
Role of Estradiol in Men



0.3% T= E2



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Balanced Estradiol in Men: Benefits

- Estradiol is involved in maintenance of proper
  - Bone density
  - Percent body fat
  - Erectile Function and Penile Sensitivity
  - HDL cholesterol
  - Cognitive function/mood
  - Inflammation modulation

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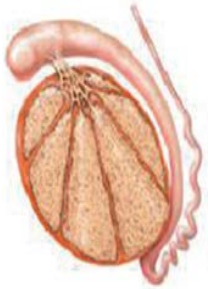
Role of estrogen in male reproduction

Estrogen Receptors in the pre-optic area and anterior hypothalamus have high levels of aromatase and estrogen receptors which regulate libido.

The penile vasculature and urothelium are lined with Estrogen Receptors

Role of Estrogen in Male Reproduction



Leydig, Sertoli and Germ cells all produce estrogen at various stages of testes development leading to testosterone modulation. An inappropriate increase in estradiol leads to a decrease in testicular size and sperm production

Figure by Vannesa Dudley

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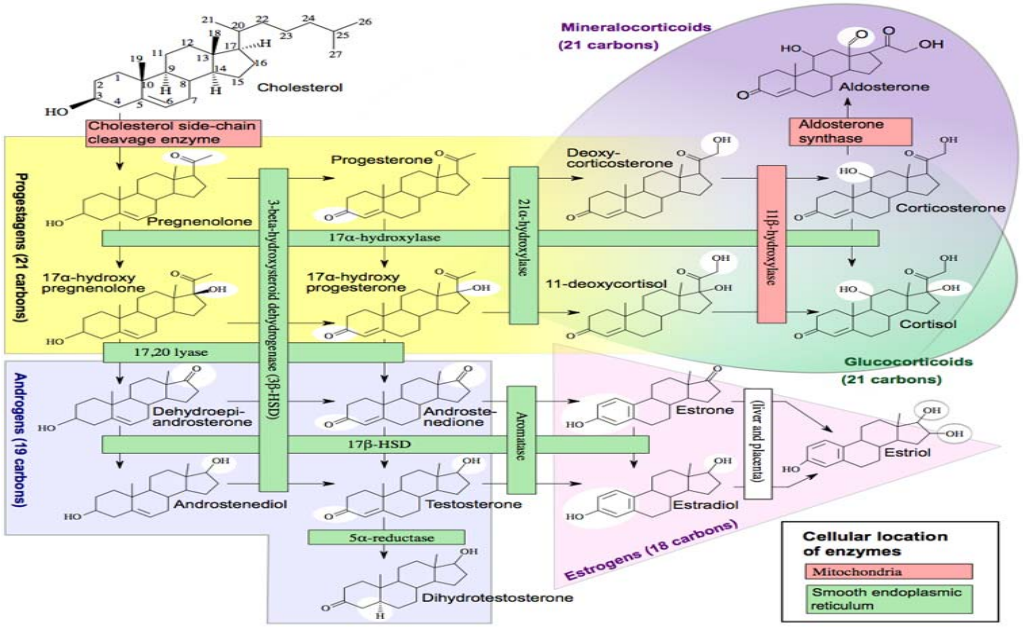
Role of Estradiol in Men: Bone

- Longitudinal studies have shown that low total and bioavailable E2 levels are associated with increased rate of bone loss, with increased risk at a threshold of 40 pmol/L [*].
- Androgen deprivation therapy with GnRH agonists for prostate cancer, which leads to dramatic reductions in both T and E2, leads to a decrease in bone mineral density of up to 13% annually and an increased risk of fracture [**].

[*] Khosla S, Melton J, Atkinson EJ, O'Fallon WM. Relationship of serum sex steroid levels to longitudinal changes in bone density in young versus elderly men. J Clin Endocrinol Metab 2001;86:3555–61
[**] Guise TA, Oefelein MG, Eastham JA, Cookson MS, Higano CS, Smith MR. Estrogenic side effects of androgen deprivation therapy. Rev Urol 2007;9:163–80

Estrogen Types

- Three Types: Estradiol, Estrone and Estradiol
- Estradiol is strongest and made in ovaries, testicles, liver and fat cells
- Estrone is 50-70% less active than estradiol and made mainly in fat cells
- Estriol is only 10% as estradiol, made in the liver and cannot be coverted to estrone or estradiol.



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Estrogens in Men: E1, E2 and E3

- There is significant inconsistency and confusion over the clinical importance of estrogens with regard to sexual function.
- Endogenous estrogens in humans are found as estrone (E1), 17b-estradiol (E2), and estriol (E3)
- Of all known estrogens, **E2 has the highest affinity for the estrogen receptors (ERs) and is the most biologically active** [*].

[*] Boothby L. Bioidentical hormone therapy: A review. Menopause 2004;11:356–67

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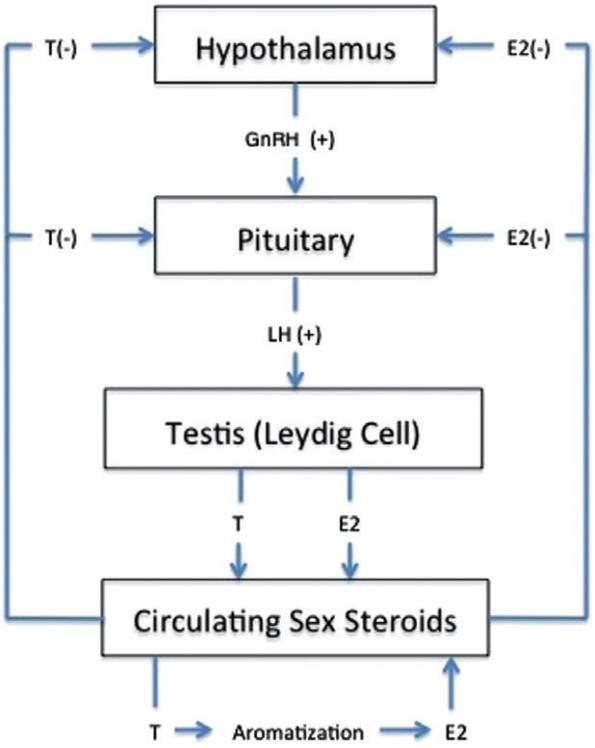
Inhibitory effect of E2 on the hypothalamic–pituitary–gonadal axis and endogenous T production

There is substantial evidence that estrogen signaling via the hypothalamic–pituitary–gonadal (HPG) axis plays an important role in controlling gonadotropin-releasing hormone (GnRH) and gonadotropin secretion in men.



Inhibitory effect of E2 on the hypothalamic– pituitary–gonadal axis. E2 = estradiol; GnRH = Gonadotropin-releasing hormone; T= testosterone

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Epidemiology of Estrogens in Men

- Compared with T, E2 is an approximately 200-fold more potent inhibitor of gonadotropins (LH and FSH) [*].
- As T is the substrate for approximately 80% of serum E2
- It should be noted that most clinical studies have used commercially available immunoassays, which may have limited precision and accuracy for measurement of lower E2 levels compared to newer LC/MS assays [**].

[*] Finkelstein JS, O'Dea LS, Whitcomb RW, Crowley WF. Sex steroid control of gonadotropin secretion in the human male II effects of estradiol administration in normal and gonadotropin-releasing hormone-deficient men. J Clin Endocrinol Metab 1991;73:621–8
[**] Middle JG, Kane JW. Oestradiol assays: Fitness for purpose? Ann Clin Biochem 2009;46:441–56.

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Where are Estrogens Produced in Men?

- In men, E2 is the best studied estrogen and is primarily produced via peripheral aromatization of serum T. However, about **20% of serum E2 in men is produced by Leydig cells in testicles**. The rest is produced in aromatase-rich fat and liver cells. Aromatization of the adrenal androgen androstenedione produces E1, a small portion of which is converted to E2 [*]
- It is important to recognize that estrogen may be produced, metabolized, and have local paracrine effects in target tissues, without necessarily affecting serum estrogen levels.
- A substantial fraction of E2 is bound to sex-hormone binding globulin (SHBG) and this fraction is not considered to be biologically active. SHBG binds E2 less avidly than T

[*] Saez JM, Morera AM, Dazard A, Bertrand J. Adrenal and testicular contribution to plasma oestrogens. J Endocrinol 1972;55:41–4

Accuracy of E2 Blood Test

- Importance of lab methodology and the sensitive E2 test in men
  - Electrochemiluminescence immunoassay (ECLIA) overestimates estradiol because of interference with C-Reactive Protein (CRP) (inflammation).
  - Testing with Liquid chromatography/mass spectrometry (LC/MS) accurately measures E2 and free E2 (and most hormones).

Causes of High Estradiol

- Estradiol Treatment
- Increased Aromatization of T to E2
- Genetic mutations or aromatase enzyme excess
- Low T/E2 ratio: Testosterone blockage (prostate cancer)
- Medications (anti-seizure meds, HIV meds, etc)
- Higher BMI
- Older age?
- Other hormone effects
- Certain foods?
- Environmental toxins
- Certain micronutrient deficiencies?

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Estrogen Receptors Alpha and Beta are Everywhere

- The two best-characterized estrogen receptors (Ers) are ER-alpha and ER-beta. They are found in a variety of tissues in both genders including **brain, liver, fat, lung, bladder, and bone marrow** [*].
- Histologic studies have also found both ERs in **corpora cavernosa, neurovascular bundles, urethra, seminal vesicles, and prostate** [**], although ERb generally dominates in urogenital tissues [***].
- **The individual role of ERa and ERb are not known.**

[*] Nilsson S, Gustafsson JA. Estrogen receptors: Therapies targeted to receptor subtypes. Clin Pharmacol Ther 2011;89: 44–5
[**] Mowa CN, Jesmin S, Miyauchi T. The penis: A new target and source of estrogen in male reproduction. Histol Histopathol 2006;21:53–67
[***] Saunders PT, Sharpe RM, Williams K, Macpherson S, Urquart H, Irvine DS, Millar MR. Differential expression of oestrogen receptor alpha and beta proteins in the testes and male reproductive system of human and non-human primates. Mol Hum Reprod 2001;7:227–36

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Potential Symptoms of High Estradiol

- Nipple sensitivity
- Fluid retention? No studies with use of anastrozole to decrease androgen associated edema.
- Low mood? . One study
- Decreased libido. Some evidence
- Increased venous leakage?. Small pilot study

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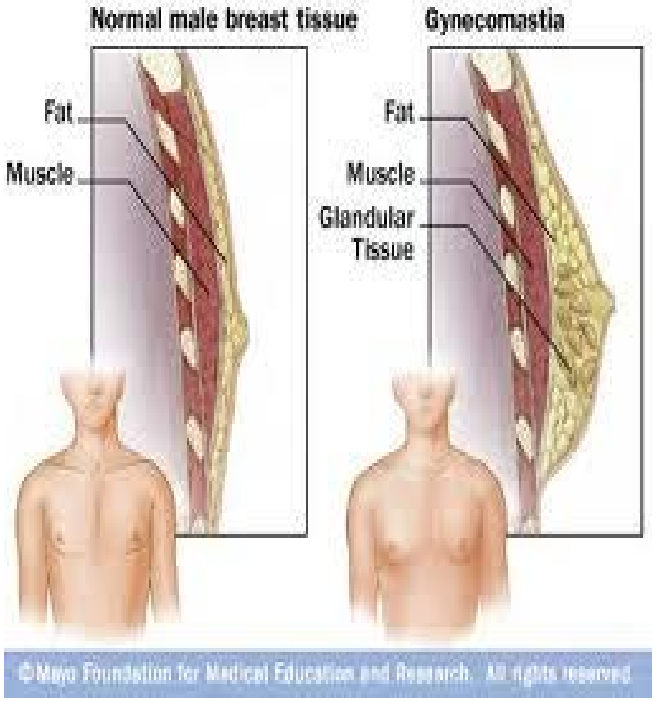
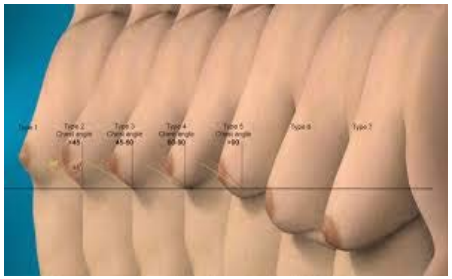
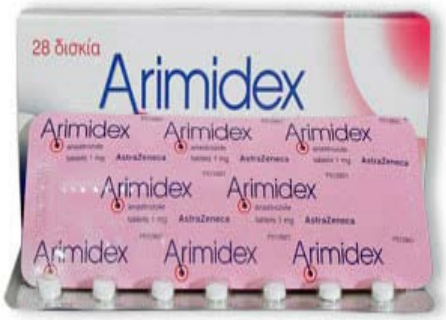
Gynecomastia
(breast enlargement in men)





Treatment: Estrogen Blocker Medications or surgery (in worst cases)



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Gynecomastia: Potential Hormone Factors.
It's nerver one hormone!

- Gynecomastia can be affected by:
  - Low T, high E2. Low T/E2 ratio?
  - Low DHT, high E2
  - Normal-high T, high E2, high IGF-1
  - None of the above unless there is a genetic polymorphism present
  - What is "High E2"? Should the level of T determine that value?
  - What's a good range for E2? 20-50 pg/mL?

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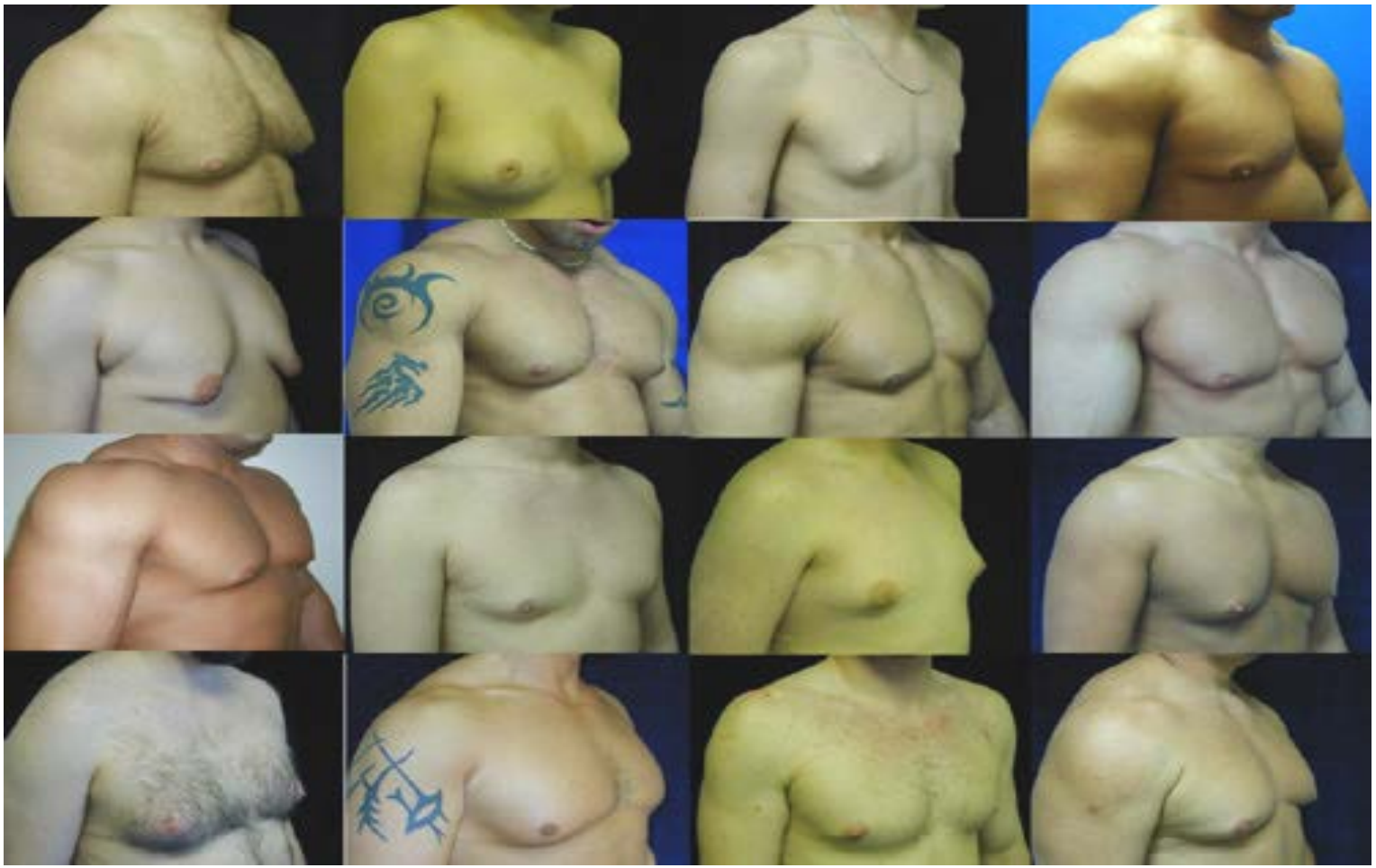
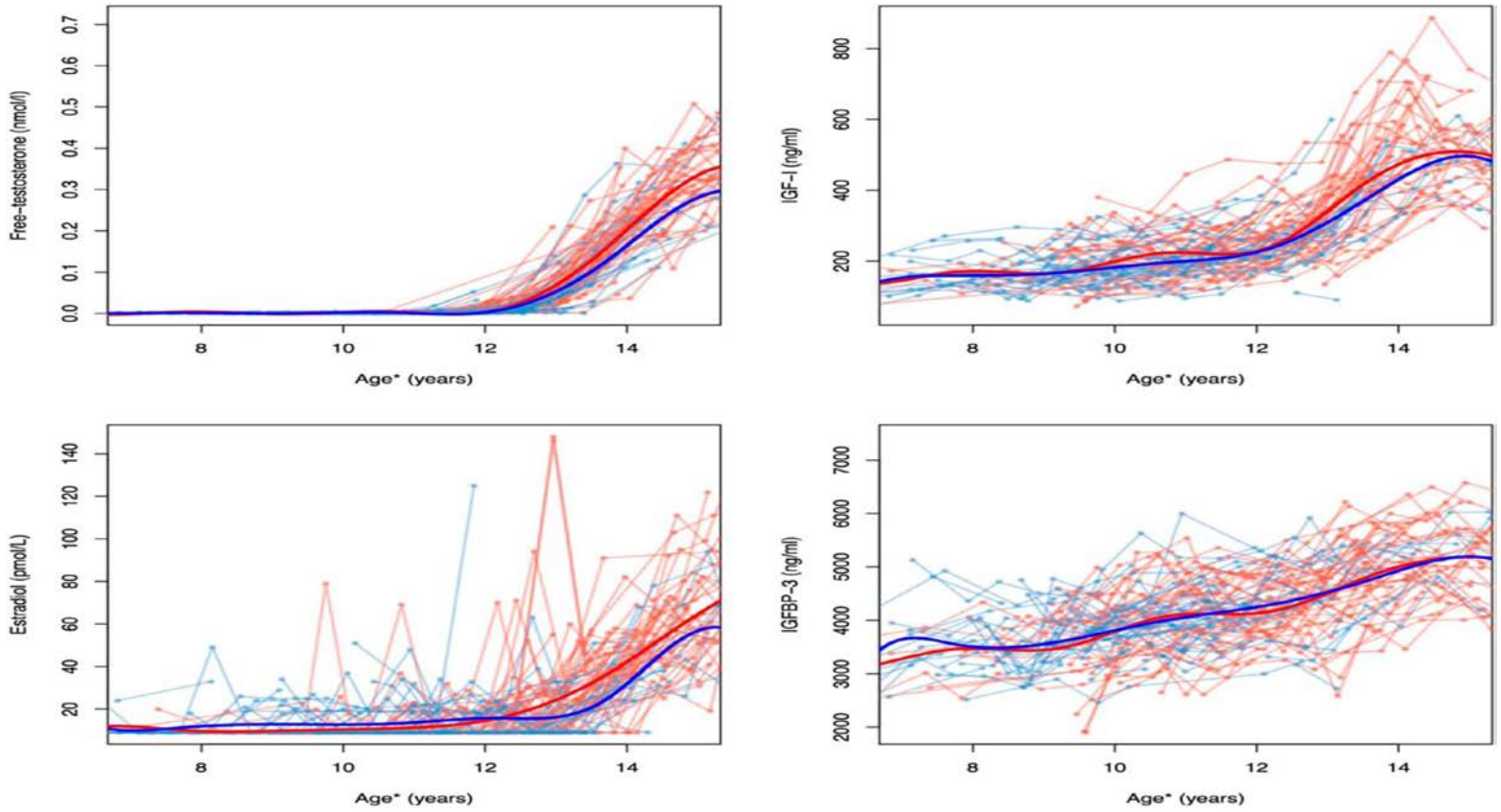
Examples of Different Gynecomastia Cases



Courtesy of Dr Rick Silverman

A Longitudinal Study of Growth, Sex Steroids, and IGF-1 in Boys With Physiological Gynecomastia



Conclusion: Gynecomastia is frequent in pubertal boys. Increased IGF-1 levels and pubertal growth appear to be associated, whereas changes in estrogen to testosterone ratio seem negligible.

Mieritz et al; *The Journal of Clinical Endocrinology & Metabolism* **2015,** 100, 3752-3759.

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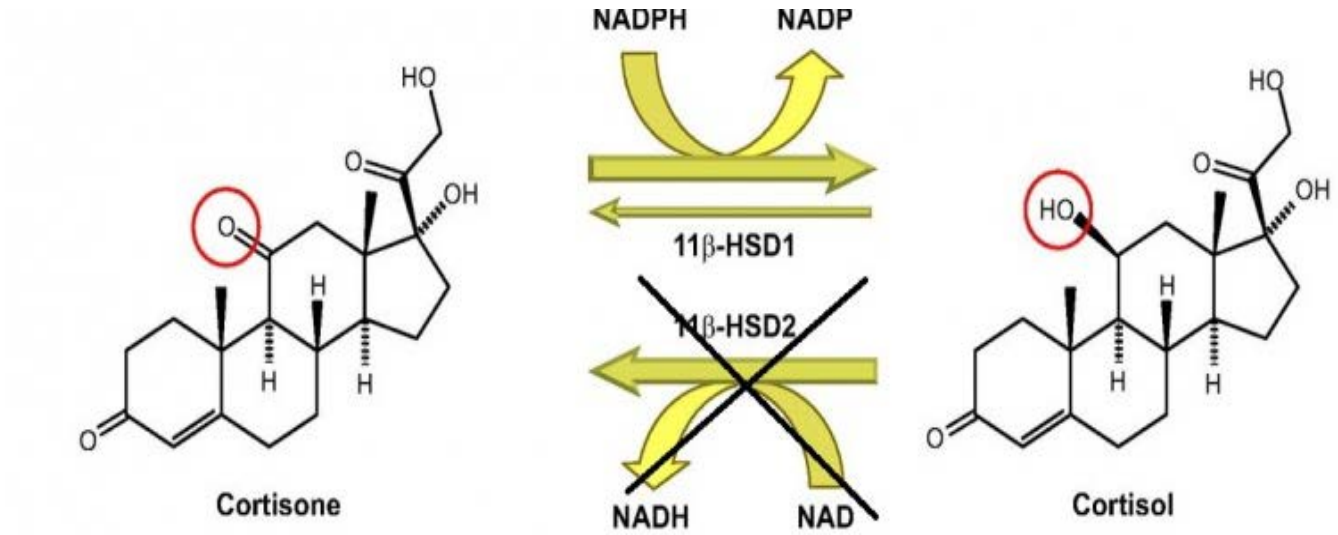
TRT-Related Water Retention: Is it Caused by High Estradiol?

- Testosterone can inhibit the enzyme 11 beta- hydroxysteroid dehydrogenase 2 that helps deactivate cortisol into cortisone.
- Increased cortisol increases sodium retention. Water retention causes high BP.
- Increased sodium and water retention on TRT may occur even with low E2
- No data on the use of anastrozole and water retention



Fürstenberger C., et al. Toxicological Sciences, Volume 126, Issue 2, 1 April 2012, Pages 353–361

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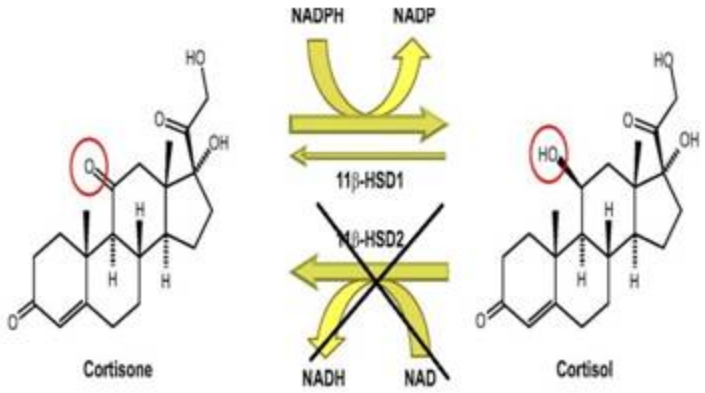
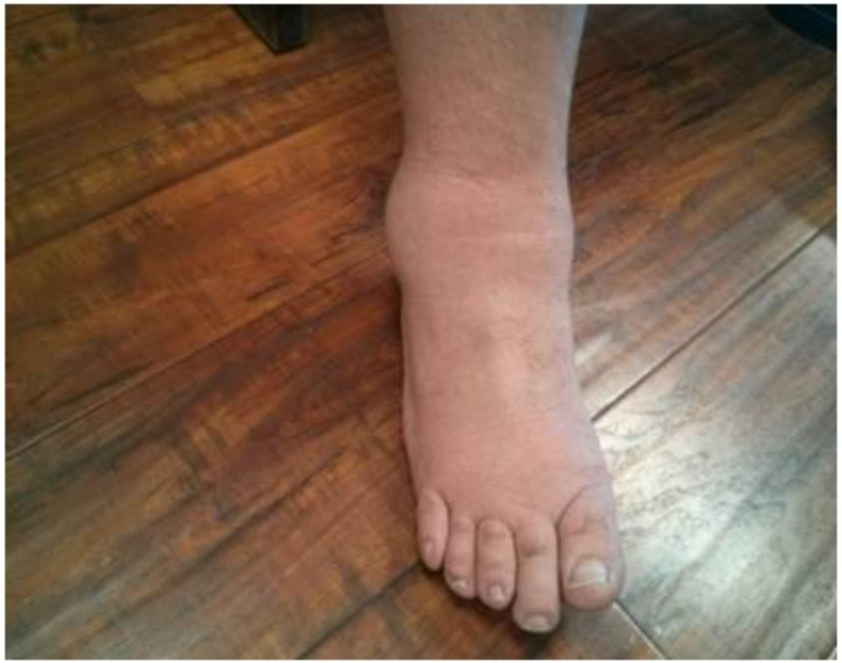
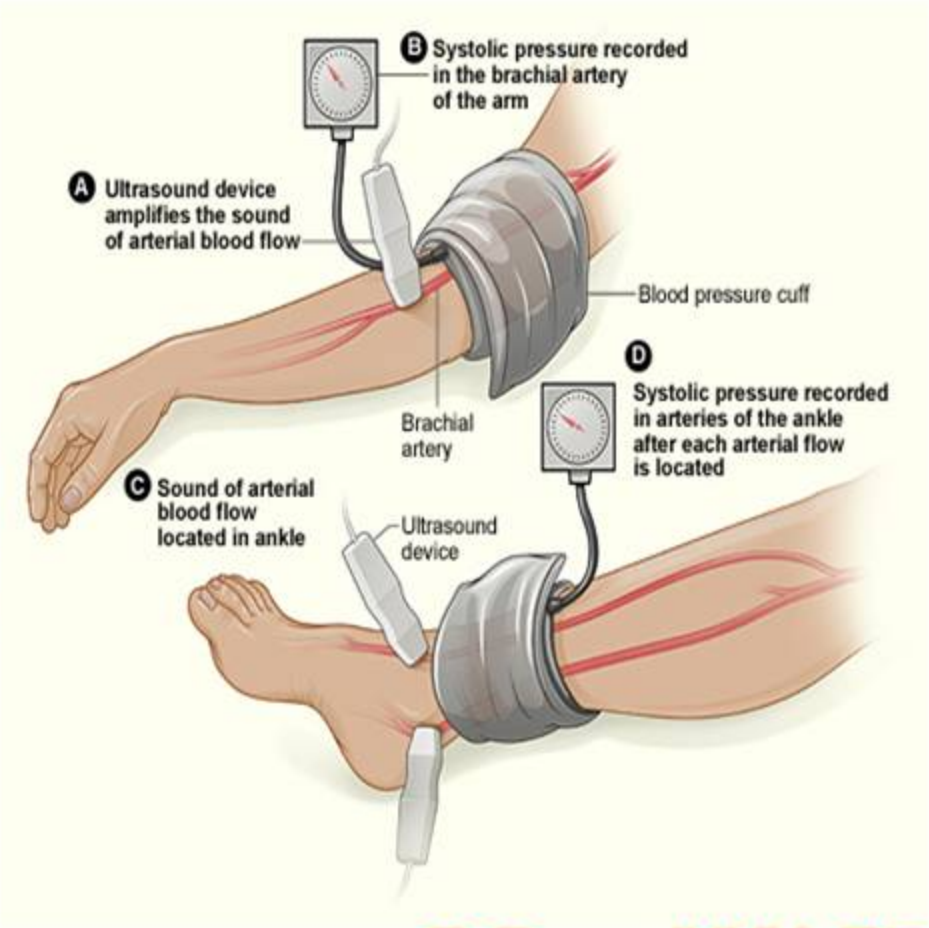
TRT-Induced Lower Extremity Edema: Concerns for Pheripheral Artery Disease







Estradiol Response in Testosterone Therapy Trials

Trial	Subjects	Intervention	Baseline E2	Impact on E2	Comment
Allan et al. [97]	60 men aged > 55 with T < 15 nmol/L and BMI < 30	**RCT (52 weeks)** **1) Androderm 5 mg daily** **2) Placebo**	1) 50.9 ± 4.1 pmol/L 2) 53.6 ± 5.0	↔	No significant change in E2. Specific values not reported.
Amory et al. [98]	75 men aged > 65 with T < 12.1 nmol/L	**RCT (36 months)** **1) T enanthate 200 mg IM q 2 week** **2) T + finasteride** **3) Placebo**	1) 83.3 ± 44.4 2) 71.5 ± 33.7 3) 84.0 ± 33.3 pmol/L	↑	Significant increase in E2 for all men receiving T. Greater increase in E2 for men receiving both T and finasteride. Specific values not reported.
Chiang et al. [99]	38 men aged 20–75 with T < 300 ng/dL or FT < 8.7 pg/mL	**RCT (3 months)** **1) Daily androgel 5 g** **2) Placebo**	1) 46.1 ± 23.7 2) 52.1 ± 16.0 pg/mL	↔	1) 54.5 ± 24.7 2) 2) 47.3 ± 21.8 Nonsignificant increase in E2
Reyes-Vallejo et al. [100]	211 men, mean age 55.2 ± 9.7, with T < 300 ng/dL or FT < 1.5 ng/dL	**Retrospective study: gel (137 points), T enanthate (65), patch (8), buccal (1)** **1) T levels: 0–200** **2) 201–300** **3) 300+**	All: 26.0 ± 9.93 pg/mL 1) 21.3 ± 12.9 2) 28.3 ± 10.8 3) 26.7 ± 7.85	↑	Specific values for each group not provided. Mean increase of 2.37 pg/mL in E2 for all subjects.
Schubert et al. [101]	40 men aged 18–64 with T < 5 nmol/L	**RCT (30 weeks)** **1) T ethanate 250 mg q 3 weeks** **2) 2) T undecanoate 1,000 mg q 6–9 weeks** **3) Prolonged TRT (N = 32): T undecanoate** **4) 1,000 mg q 8–12 weeks**	1) 23.1 ± 4.96 2) 2) 21.6 ± 6.91	↑	1) 27.5 ± 9.33 2) 2) 29.6 ± 8.02 E2 rose in parallel with T. Decline in E2 over time with prolonged TRT.

BMI = body mass index; E2 = estradiol; FT = free testosterone; IM = intramuscular; RCT = randomized controlled trial; T = testosterone; TRT = testosterone therapy

DOI: 10.1111/j.1743-6109.2012.02726.x

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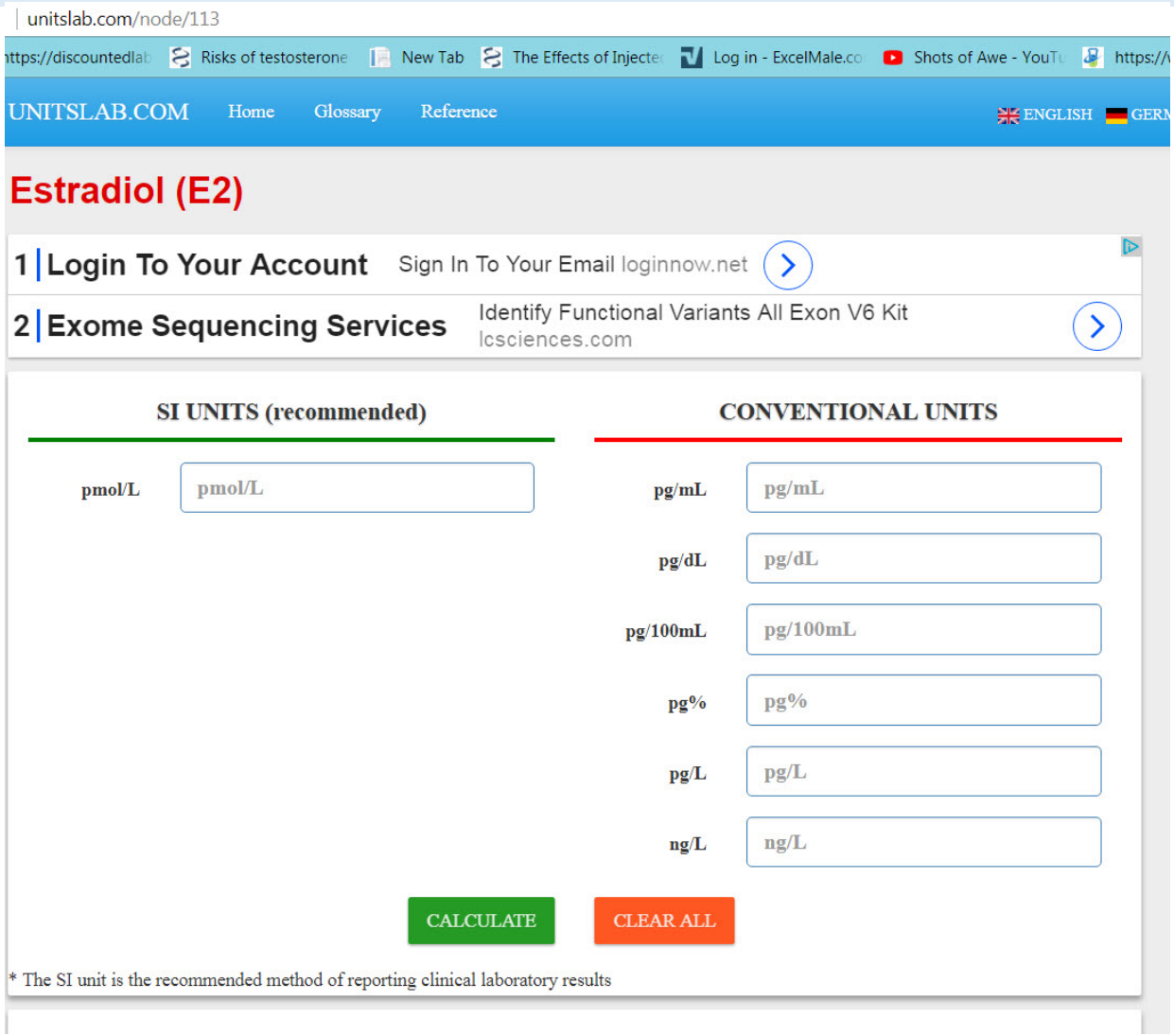
Estradiol Unit Conversion Site



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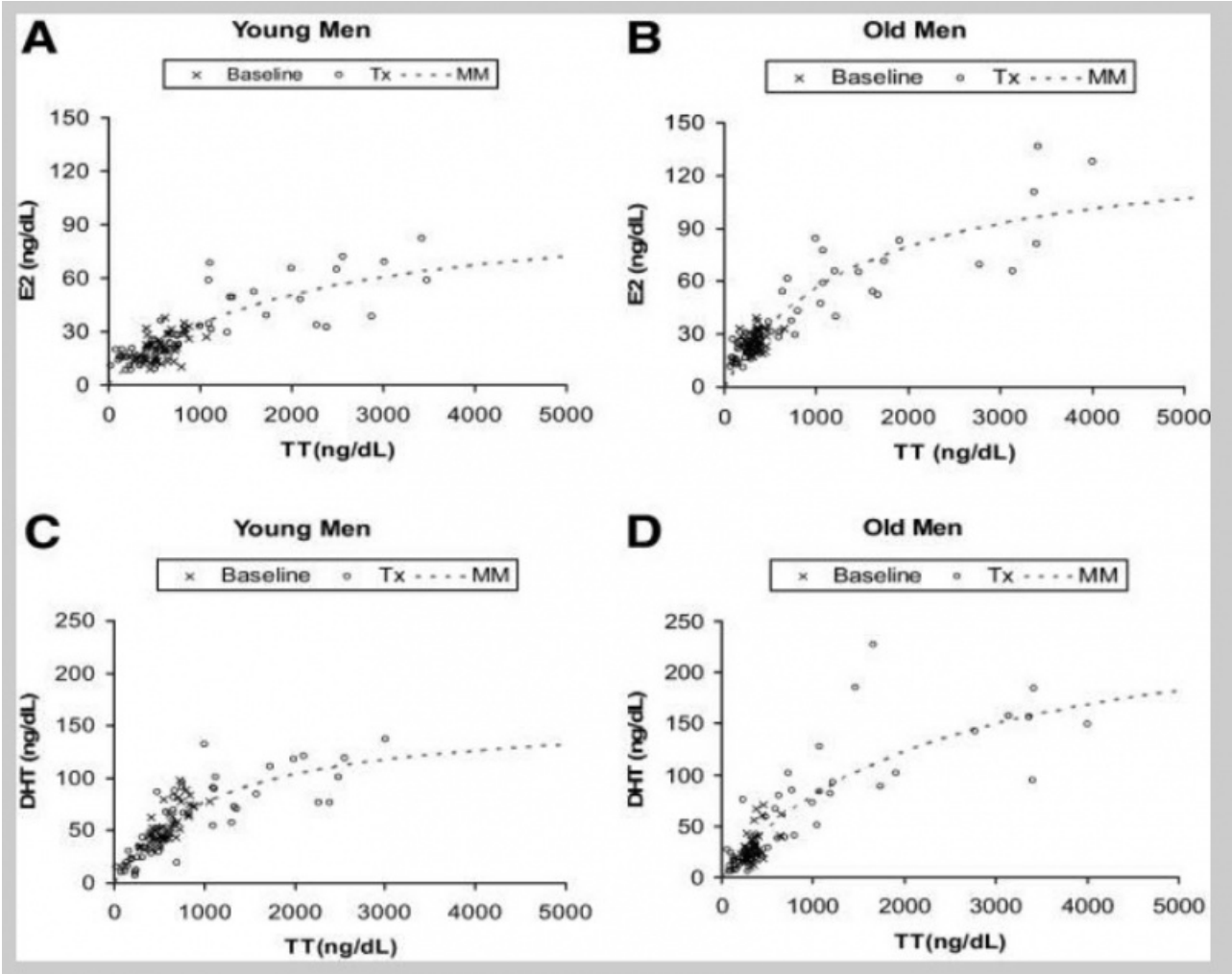
The Effects of Injected Testosterone Enanthate Dose and Age on the Conversion of Testosterone to Estradiol and Dihydrotestosterone in Young and Older Men

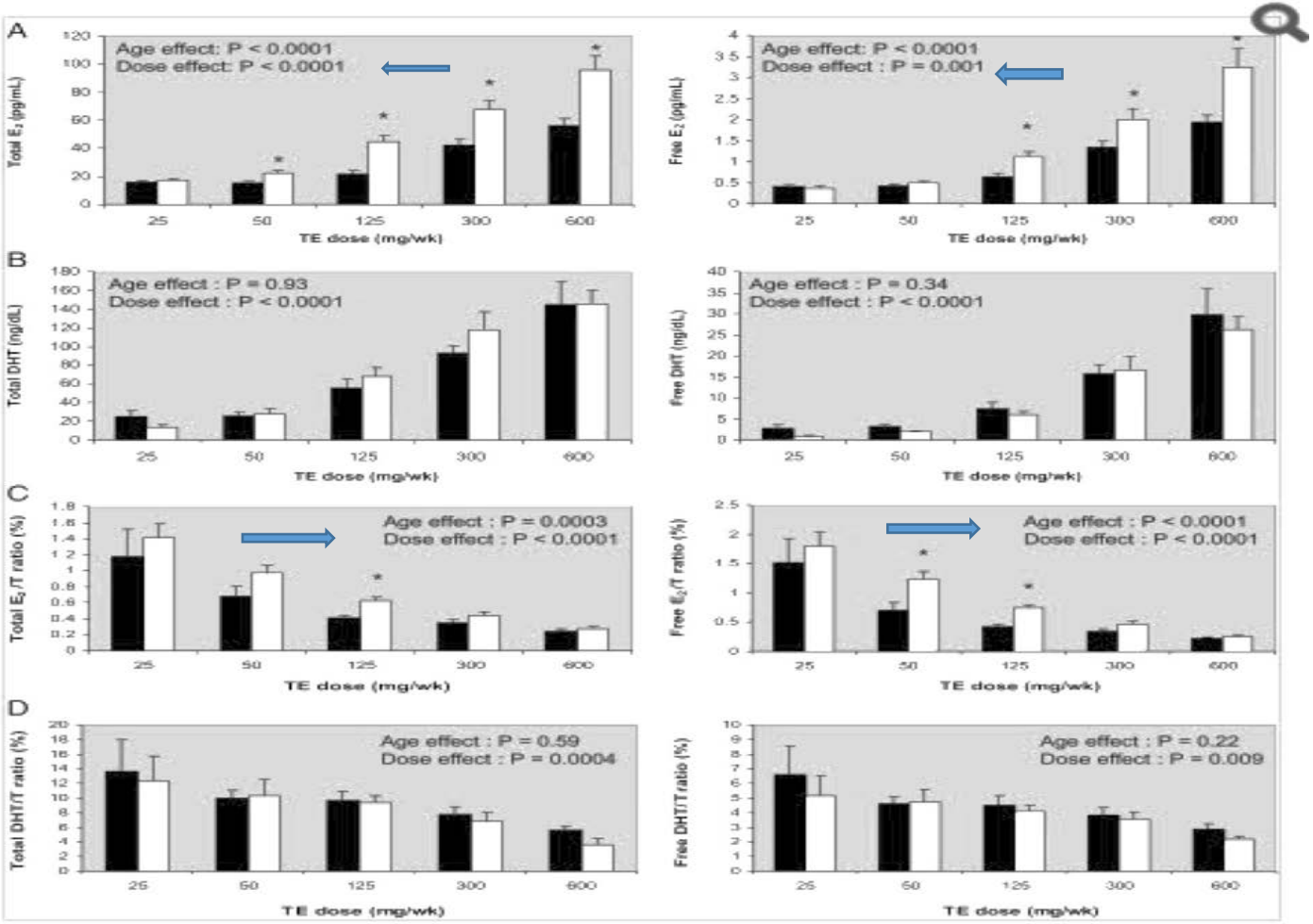


J Clin Endocrinol Metab. 2010 Aug; 95(8): 3955–3964.

Effect of Different Testosterone Enanthate Injection Doses on Estradiol and DHT (Young and Older Men)

Black Box: Young

White Box: Older



J Clin Endocrinal Metab. 2010 Aug; 95(8): 3955-3964.

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High Estradiol Management

- Several physicians prescribe **anastrozole** if estradiol by sensitive test is over 40-50 pg/mL at follow up.
  - 0.5-1 mg/week is the usual starting dose to be readjusted at second follow up visit.
  - Several physicians also prescribe doses as high as 1 mg/day.
  - Some even prescribe anastrozole when starting TRT irrespective of baseline estradiol
  - Many physicians are still dosing based on the wrong E2 test
- Tamoxifen has been shown in studies to be more effective at reversing early to moderate gynecomastia than anastrozole. It does so by decreasing estradiol and IGF-1. More on this later.
- No data on the use of other SERMS beyond clomiphene for improved testosterone/estradiol ratios
- Surgery may be required for advanced cases that do not respond to treatment.
- Should we be monitoring or treating based on T/E2 ratio?

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Anastrozole in Testosterone Treatment

- Most men on TRT do not need anastrozole unless they are high aromatization due to genetic or other factors.
- Emphasize to patients the goal of testosterone treatment is to optimize T levels and control estradiol levels between 20 pg/ml and 50 pg/ml. Use sensitive estradiol test (LC/MS)
- It is recommended to avoid estradiol levels below 20 pg/mL. This may be linked to low bone density, higher fat content and lower sex drive. Estradiol may also have a role in cognitive function.
- Usually, higher fat mass will increase estradiol. Many men can taper down dosage of anastrozole after a period of time during treatment due to fat loss. Less fat means less aromatization of testosterone to estradiol.
- Insurance doesn't cover anastrozole for a male indication as it is gender specific for women with breast cancer. Compounding pharmacies sell it cheaply.

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Anastrozole (Arimidex) To Control Estradiol Levels in Testosterone Treatment

- Breast cancer drug used off label in men to control E2 levels
- Anastrozole is the best single, reliable way to control E2 levels.
  - Other supplements Zinc 50mg/Copper 2-3 mg, Chrysin 1000mg, work well in some patients but not as reliable as the gold standard of anastrozole.
- Compounded anastrozole available
  - 1 , 0.5 and 0.25 mg capsules
  - Dose range – 0.5 to 1.0 mg per week in men with over E2 of 40 pg/mL at week6 or 8 follow up. Adjust dose based or second follow up
  - Many men may not need anastrozole treatment
  - Patients can be instructed to take as needed if sensitivity develops in nipples.
  - Some physicians prescribe anastrozole at start of TRT independent of baseline estradiol blood level

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Estradiol Inhibition with Anastrozole

- Arimidex is very powerful and higher dosages (1 mg/day) will lower "estradiol by approximately 70% within 24 hours and by approximately 80% after 14 days of daily dosing." [1]

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Anastrozole monotherapy increased T but did not improve symptoms in men with low T

- In another study, 88 men with low T over 60 years were randomized to anastrozole or placebo.
- At baseline, all men reported symptoms of low T as determined by the Androgen Deficiency in Aging Males (ADAM) questionnaire.
- For men treated with anastrozole, T levels peaked after 3 months and were still significantly increased over baseline and placebo at 12 months.
- After 12 months of treatment, 11 of 44 patients receiving a placebo reported resolution of symptoms of low T, compared with only seven of 44 patients receiving anastrozole. Furthermore, patients treated with anastrozole did not have changes in body composition or muscle strength, or an increase in hematocrit, as would normally be seen in TRT studies [*].
- It is worth noting that in this one study sexual symptoms were not improved despite normalization of serum T

[*] Burnett-Bowie AM, Roupeniean KC, Dere M, Lee H, Leder B. Effects of aromatase inhibition in hypogonadal older men: A randomized, double-blind, placebo controlled trial. Clin Endocrinol (Oxf) 2009;70:116–23..

Tamoxifen or Raloxifene (SERM)

For boys and men with severe gynecomastia that is causing substantial tenderness or embarrassment, a short course of tamoxifen (sample brand name: Nolvadex, 20 mg daily for 3-6 months) or raloxifene (brand name: Evista, 60 mg every other day) may be recommended.

These drugs block the effects of estrogen in the body and can reduce the size of the breasts somewhat. However, neither of these drugs is approved in the United States for the treatment of gynecomastia, but they can be prescribed off-label and purchased at compounding or regular pharmacies.

Other Estradiol Blockers

1. Letrozole (Femara). One study (in women) showed that Arimidex could achieve almost total suppression of estradiol levels but was still detectable. However, letrozole was even more powerful and could achieve total suppression of estradiol to where it could not even be detected! [2] Be careful in going too low with estradiol as it can actually lead to osteoporosis, body aches, mood, and erectile issues, etc

However, in some cases, that slight extra horsepower from letrozole can help with gynecomastia, at least according to the "common knowledge" on the steroid forums. The general feedback is that anastrozole can prevent gyno usually, but letrozole can actually reverse it (in some cases). Discuss with your physician of course as letrozole has a reputation for more side effects.

2. Suicide Inhibitors (such as Aromasin). These "type I" type of aromatase inhibitors do their work using a little different technique: they actually bind to the aromatase enzyme and permanently and irreversibly take it out of commission. This may seem really concerning, but the body rebuilds those enzymes after a few weeks. These type of inhibitors are popular in the steroid community on their own. It may also have mild androgenic properties

   One study on young men showed that 25 and 50 mg dosages both reduced plasma estradiol levels by about a third in 14 days[3]

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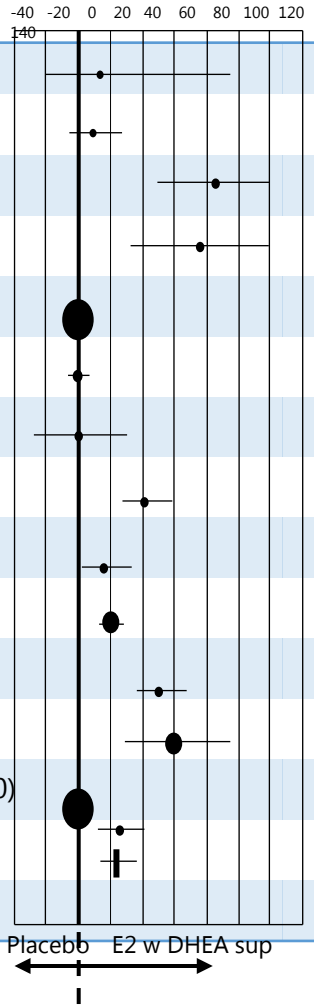
DHEA Supplementation and Estradiol

Weighted standardized differences (with 95% confidence interval) of E2 at endpoint across RCTs evaluating the effect of DHEA vs Placebo therapy

E2 mean differences (pmol/L)

Source	Diff. In mean	LL, 95% CI	UL, 95% CI	P
Nestler et al.,1988 (12)	9.40	-6.60	25.40	0.25
Morales et al.,1994 (13)	26.00	-20.46	72.46	0.273
Flynn et al., 1999 (16)	85.81	50.32	121.30	0.000
Flynn et al., 1999* (16)	77.94	34.86	121.02	0.000
Baulieu et al., 2000 (18)	1.67	-8.09	11.42	0.738
Arlt et al., 2000 (18)	1.00	-6.71	8.71	0.799
Jedrzejuk et al., 2001 (19)	2.57	-27.60	32.75	0.867
Villareal et al., 2004 (24)	41.18	23.65	58.70	0.000
Martina et al.m 2006 (26)	16.00	3.45	28.55	0.012
Nair et al., 2006 (27)	20.00	10.62	29.38	0.000
Villareal et al., 2006 (28)	50.40	34.30	66.50	0.000
Jankowski et al., 2008 (29)	59.50	27.75	91.25	0,000
Von Muhlen et al., 2008 (30)	3.00	-7.58	13.58	0.578
Weiss et al., 2009 (33)	23.16	8.81	37.52	0.002
Overall	24.76	14.14	35.39	0.000



Corona G et al. JCEM 2013;98:3615-3626

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hCG's Effect on Estradiol Stabilizes with Time

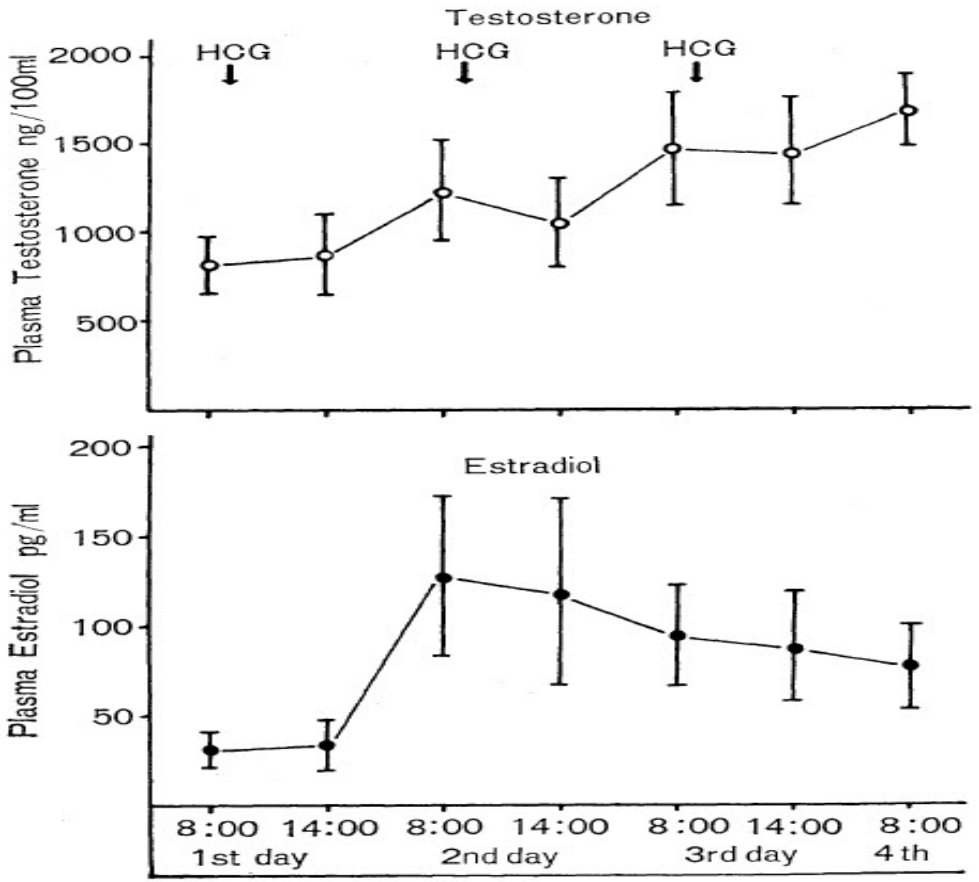

Fig. 4. Response patterns of plasma estradiol and testosterone after HCG administration to normal men. Values are expressed as mean ±SD.

Dose:
3,000 IU hCG daily
for 3 days

Ishimaru, T. Plasma Estradiol Concentrations and Effect of hCG on Plasma Estradiol and Testosterone in Normal Subjects and Patients with Endocrine Disorders. *Endocrinol. Japon.* 1975, 22 (4), 287 296

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Study: Estradiol and Sex Drive in Men

- In a study of 423 men on TRT, Dr Ramasamy at Baylor College of Medicine measured men's testosterone and estradiol levels and asked them to rate the quality of their libido using a five-point Likert scale (1= terrible, 5 = excellent).
- The researchers categorized the men as having low or high testosterone (below or above 300 ng/dL, respectively) and low or high estradiol (below 5 and above 50 pg/ml, respectively)
- **Men with high serum testosterone levels reported significantly greater libido than men with low level and those with high serum estradiol levels had significantly greater libido than subjects with low levels.**

From the March 2014 Issue of Renal And Urology Journal

Study: Estradiol and Cardiovascular Mortality

A prospective observational study at 2 cardiology centers (Poland) of **501 men (mean 58 years old)** with **chronic heart disease** who were followed for **3 years**. Cohort was divided into quintiles of serum estradiol (Avg TT 320 ng/dl. Not on TRT, used ECLIA E2 test)

Percent 3 Year Survival Rate:

quintile 1, < 12.90 pg/mL; **44.6%**
quintile 2, 12.90-21.79 pg/mL; 65.8%
quintile 3, 21.80-30.11 pg/mL; 82.4% (Control group)
quintile 4, 30.12-37.39 pg/mL; 79.0 %
and quintile 5, > or = 37.40 pg/mL. **65.9 %**

Reference: Circulating estradiol and mortality in men with systolic chronic heart failure. JAMA 2009 May 13;301(18):1892-901.

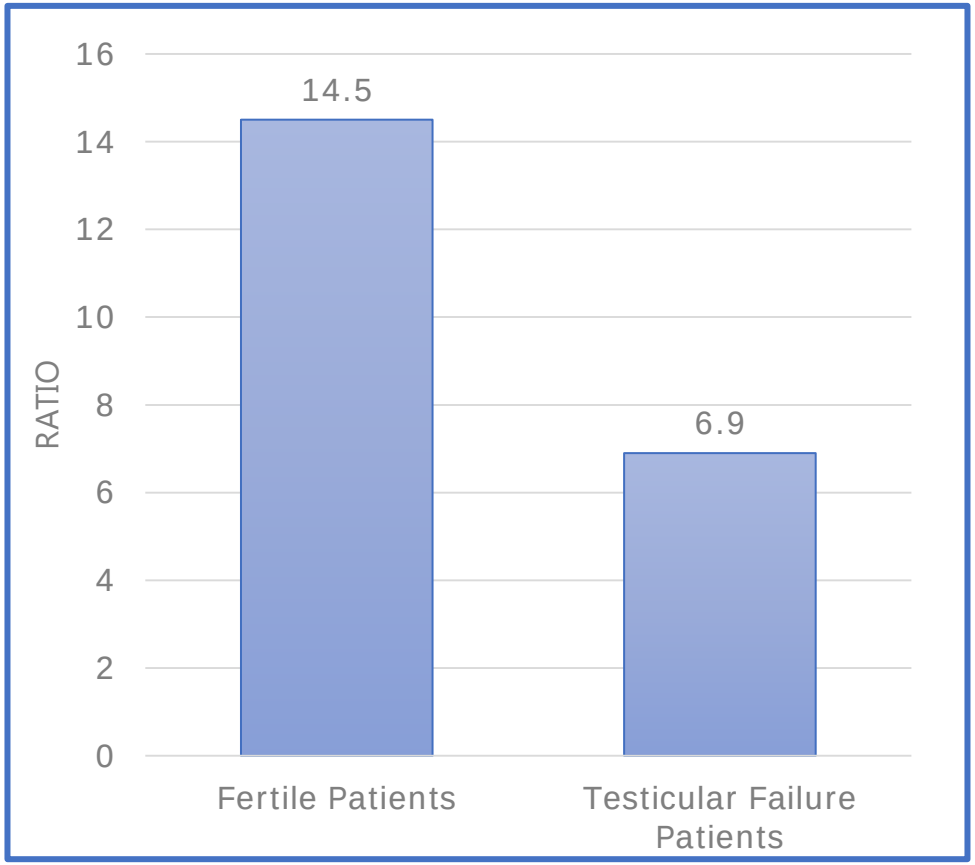
Testosterone/Estradiol Ratio In Fertile vs Unfertile Men (No Data on Libido)

T in ng/dL
divided by
E2 in pg/mL

Example:

800 ng/dL/
42 pg/mL=
19

For 14.5 ratio=
55 pg/mL E2



The Journal of Urology Volume 165, Issue 3, March 2001, Pages 837–841

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Calculated Free T and T:E Ratio but not Total Testosterone and Estradiol Predict Low Libido

- **Free T and T:E ratio were predictive of positive libido response** on IIEF11 & 12 questions in the IIEF questionnaire.
- **Estradiol, even at a cutoff of 50 pg/ml, was not independently associated with improved libido.**
- Surprisingly, **no correlation was found between total testosterone and IIEF11 (desire frequency).**
- The effect of testosterone and estradiol on libido requires further research with prospective studies.

Reference: Presented By Nikhil Gupta, Springfield, IL
at the 2017 AUA Annual Meeting - May 12 - 16, 2017 – Boston, Massachusetts, USA

Clinic Optimizers

Study: Role of Testosterone and Estradiol on Body Composition, Strength, and Sexual Function in Men

- 198 healthy men 20 to 50 years of age
- All participants received goserelin acetate (Zoladex) (a gonadotropin blocker used in prostate cancer), at a dose of 3.6 mg subcutaneously at weeks 0, 4, 8, and 12, to suppress endogenous gonadal steroids (T, E2).
- Cohort 1 and 2: 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™**) daily for 16 weeks.
- Participants in cohort 2 **also** received anastrozole (Arimidex) at a dose of **1 mg daily** to block the aromatization of testosterone to estrogen.
- Participants were unaware of the study-group assignments.

N Engl J Med. 2013 Sep 12; 369(11): 1011–1022.

Conclusion: Low Estradiol Increased Fat Mass and Decreased Gains in Libido and Erectile Function

Low blood level of estradiol was associated with **significant increases in the percentage of body fat** ($P<0.001$), subcutaneous fat area ($P<0.001$), and intra abdominal fat area ($P = 0.002$), and relative **less improvement in sexual desire** ($P<0.001$) and erectile function ($P = 0.022$)

Reference: *Gonadal Steroids and Body Composition, Strength, and Sexual Function in Men N Engl J Med 2013;369:1011-22.*

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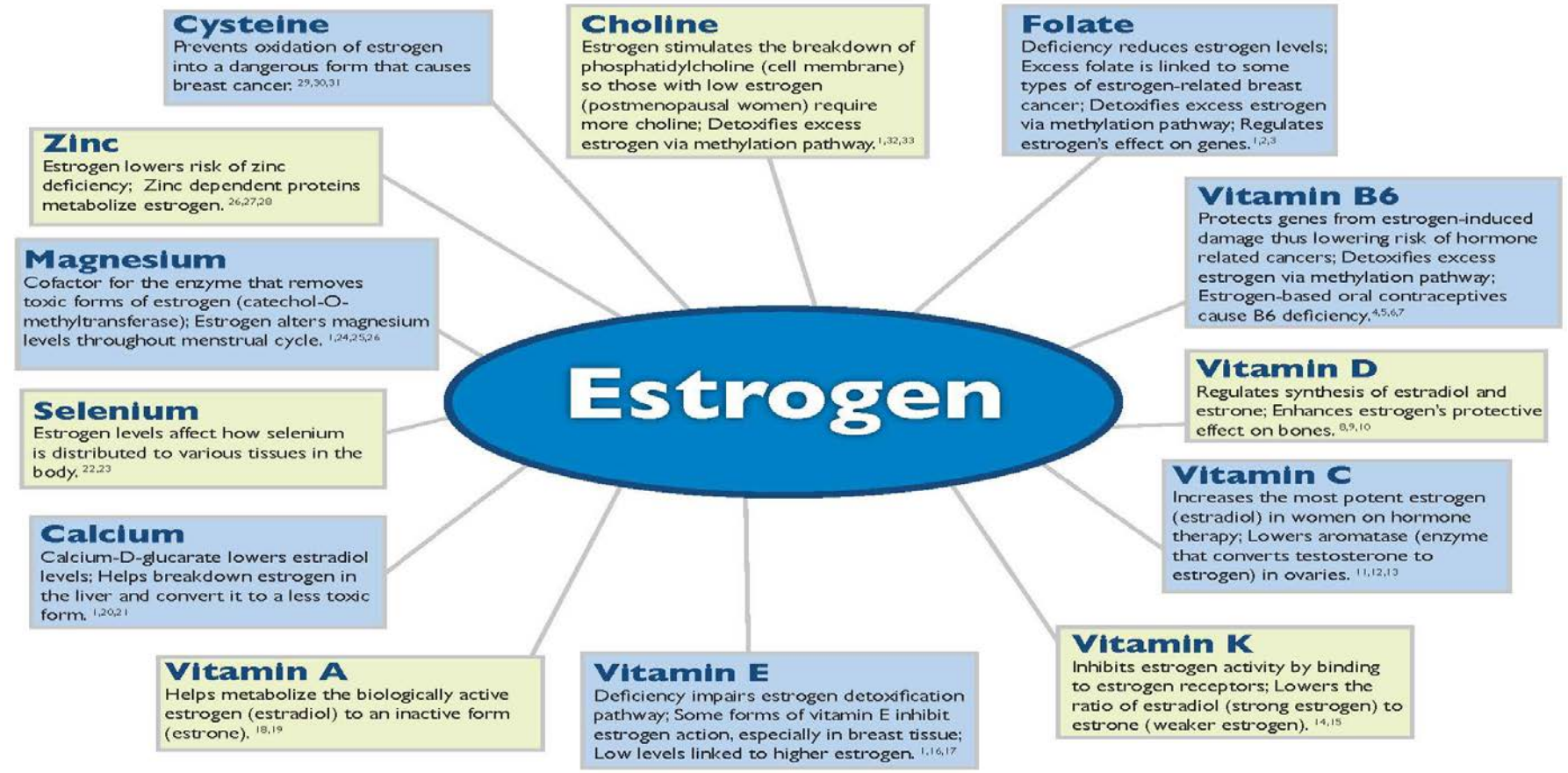
Micronutrients and Estrogen



LC/MS (Sensitive) E2 Test on DiscountedLabs.com

Estradiol (sensitive): $51

Free E2 (sensitive): $103

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Our Services

Integrative Clinical Support

Clinic Optimizers assists clinicians who are using or exploring compounding pharmacies to source medications for both clinic use and patient-specific purposes. CO offers product information, clinician education and treatment application protocols for commonly compounded prescribed medications.

Laboratory Access & Support

Clinic Optimizers can assist with hormone testing including what methodology to use, what tests to order, and how to use them to administer, titrate, and monitor hormone and related therapies. In addition, CO provides clinics with access to low cost lab testing through a nationally recognized laboratory.

Training

Clinic Optimizers offers clinicians with online training, phone consultations, and onsite training at an established clinic. Click to learn more about our in-depth training expertise.

Vendor Referral & Management

Clinic Optimizers has established relationships with key vendors that are vital to practices that focus on HRT and wellness therapies. Contact us if you would like to learn more.

Appendix 1

Gynecomastia in Males

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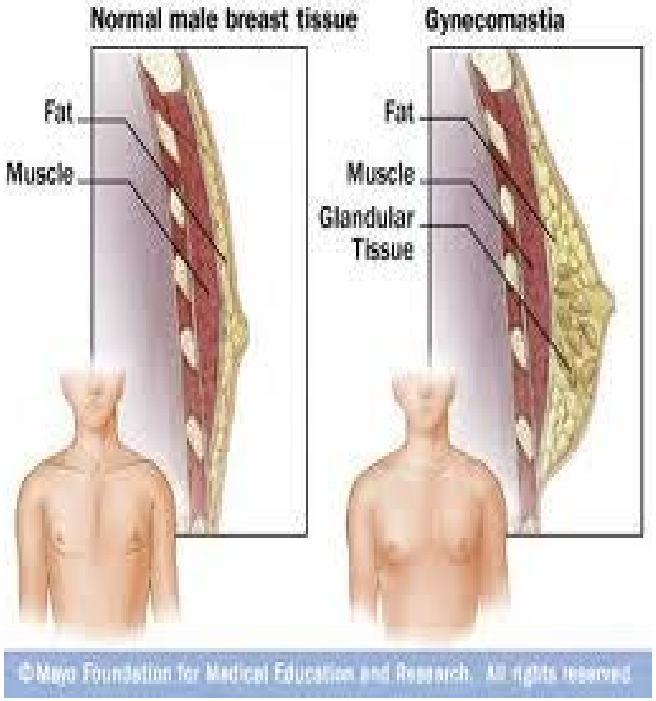
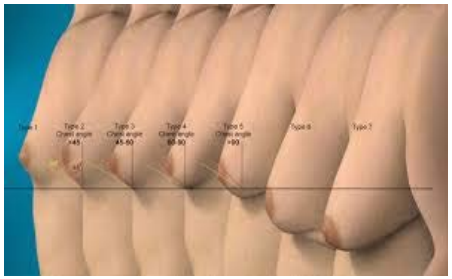
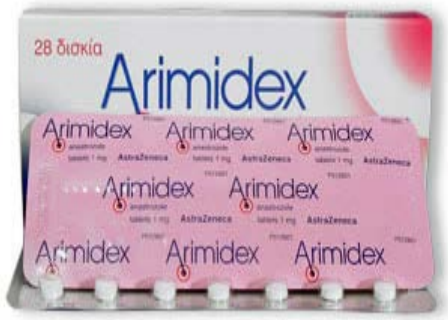
Gynecomastia
(breast enlargement in men)





Treatment: Estrogen Blocker Medications or Surgery (in worst cases)



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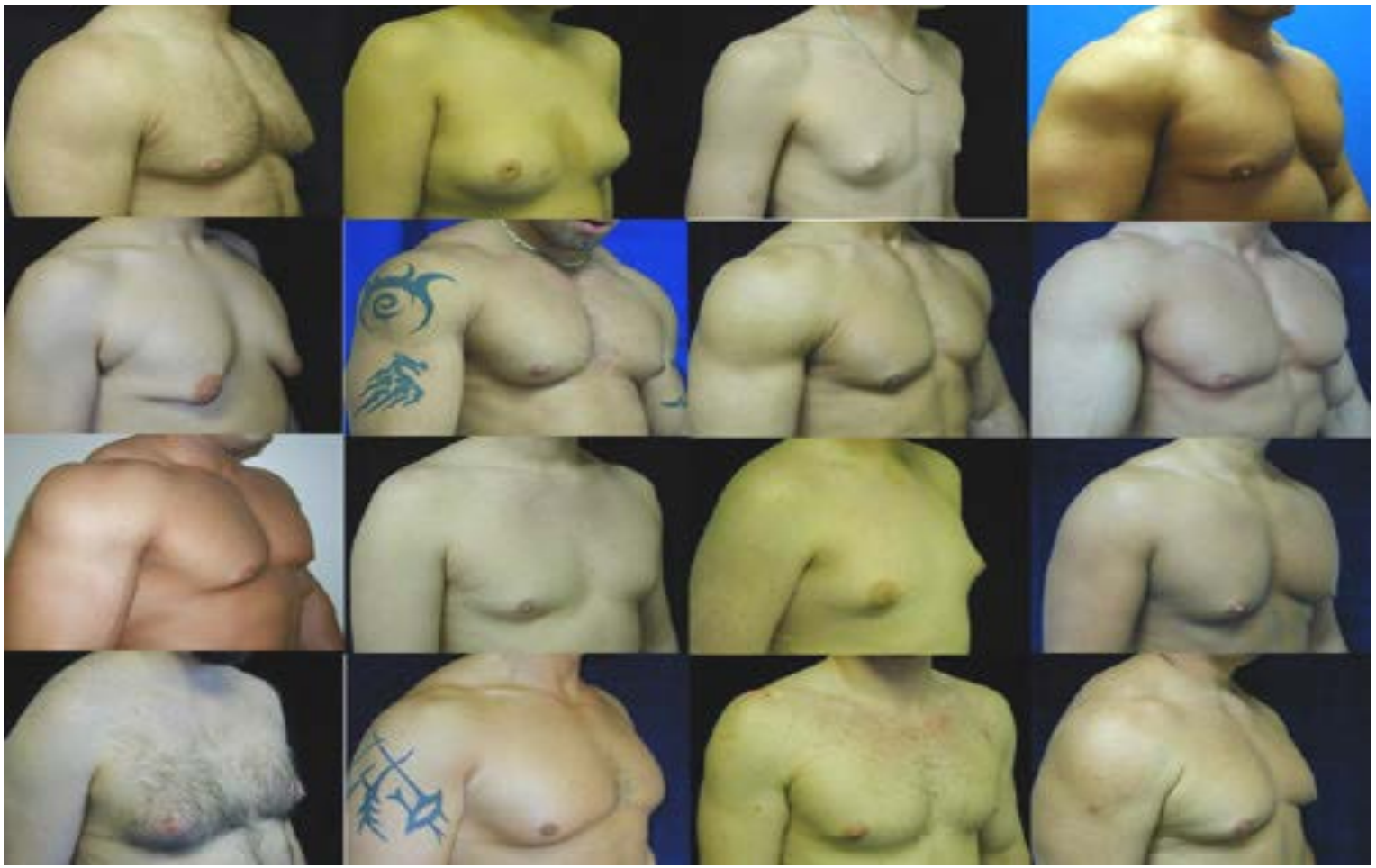
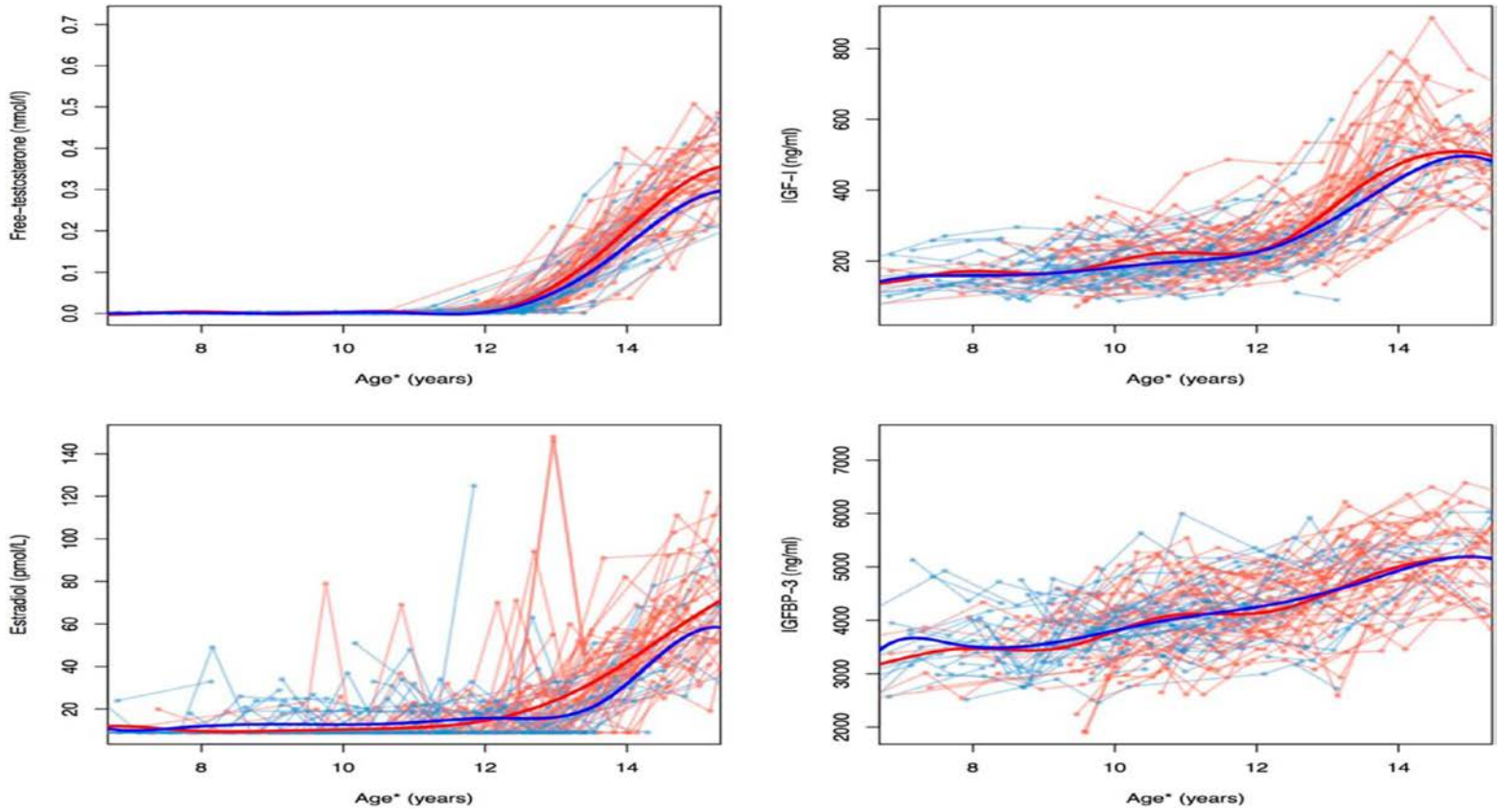
Examples of Different Gynecomastia Cases



Courtesy of Dr Rick Silverman

A Longitudinal Study of Growth, Sex Steroids, and IGF-1 in Boys With Physiological Gynecomastia



Conclusion: Gynecomastia is frequent in pubertal boys. Increased IGF-1 levels and pubertal growth appear to be associated, whereas changes in estrogen to testosterone ratio seem negligible.

Mieritz et al; *The Journal of Clinical Endocrinology & Metabolism* **2015,** 100, 3752-3759.

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Classification of gynecomastia

Definition: Enlargement of male breast tissue.

1.1. Hall 1959

- Grade I: enlargement merely palpable
- Grade II: visible enlargement
- Grade III: corresponds to a female breast

1.2. Tanner 1986

- B1: no glandular tissue palpable
- B2: enlarged areola; protruding glandular tissue
- B3: breast extends beyond the areola
- B4: increased breast size and elevation
- B5: corresponds to a female breast

PATHOGENESIS OF GYNECOMASTIA I

Absolute deficiency of androgens (hypogonadism)

- Primary hypogonadism
- Klinefelter syndrome
- Testicular trauma
- Cancer chemotherapeutic agents
- Testicular radiation
- Infections (for example, mumps orchitis, leprosy)
- Disorders in enzymes of testosterone biosynthesis: drugs (for example, ketoconazole, spironolactone, metronidazole); inherited defects in androgen biosynthesis
- Secondary hypogonadism (pituitary and/or hypothalamic damage from disease, surgery or radiation)

PATHOGENESIS OF GYNECOMASTIA II

Altered serum androgen to estrogen ratio

- Puberty
- Aging
- Refeeding gynecomastia
- Renal failure and dialysis
- Hepatic cirrhosis
- Hyperthyroidism
- Drugs (for example, ketoconazole)

Decreased androgen action

- Drugs (for example androgen blockers like spironolactone, bicalutamide, cimetidine)
- Androgen receptor defects
- Absent or defective androgen receptors (complete and partial androgen insensitivity syndromes)
- Expansion of CAG repeats in the androgen receptor gene (such as in spinobulbar muscular atrophy)

PATHOGENESIS OF GYNECOMASTIA III

Increased serum levels of estrogens or estrogen-like activity

- Exposure to exogenous estrogens (intentional or unintentional)
- Increased aromatization of androgens to estrogens (androgens, ethanol abuse)
- Estrogen agonist activity (digitoxin)

Decreased serum testosterone levels

- Hypogonadotropic hypogonadism (Low LH) (caused by gonadotropin-releasing hormone agonists/antagonists and possibly HAART therapy for HIV)
- Hypergonadotropic hypogonadism (High LH) (possible causes: destruction of inhibition of Leydig cells by chemotherapeutic/cytotoxic agents (for example, alkylating agents, vincristine, methotrexate, nitrosoureas, cisplatin, imatinib) or
- Inhibition of testosterone or DHT biosynthesis by ketoconazole, metronidazole, spironolactone or finasteride and dutasteride)

PATHOGENESIS OF GYNECOMASTIA IV

Androgen receptor blockage caused by medications

- Flutamide, bicalutamide, enzalutamide
- Cimetidine
- Marijuana
- Spironolactone
- Increased serum prolactin levels
- Antipsychotic agents
- Anti epileptic agents
- Metoclopramide
- Possibly calcium channel blockers
- Isoniazid
- Digoxin
- HAART therapy for HIV infection
- Human growth hormone
- Amiodarone
- Calcium channel blockers (for example, nifedipine, verapamil, diltiazem)
- Amphetamines

Pathophysiology of gynecomastia

Elevated estrogen levels due to increased synthesis or intake/increased estrogen effects

- Increased synthesis
  - *Direct:* caused by testicular tumors (Leydig or Sertoli cell tumor) or adrenal neoplasms.
  - *Indirect:* stimulation by HCG-producing gonadal or extragonadal germ cell tumors or non-trophoblastic tumors (lung, kidney, and liver cancer)
- Aromatization of precursors (for example, obesity, adrenal tumors)
- Increased intake (fetoplacental, topical application, occupational exposure)
- Decreased SHBG binding (for example, due to medications)

Pathophysiology of gynecomastia (2)

Decreased estrogen levels or effects

- Decreased androgen levels (primary or secondary Leydig cell failure, age-related hypogonadism, increased metabolism)
- Increased SHBG binding
- Decreased binding to androgen receptors (for example, due to medications)
- Congenital androgen receptor defect
- Pharmacological inhibition of 5-alpha reductase (finasteride and dutasteride)

Pathophysiology of gynecomastia (3)

Multifactorial

- Local estrogen sensitivity
- General disorders (obesity, chronic renal disease, liver cirrhosis, malnutrition)
- Endocrine disorders (hyperprolactinemia, hyperthyroidism)
- Pharmacological agents/drugs (see Table 3)

Mechanical

- Mechanical irritation of the breast (for example, when shooting a rifle)

Pharmacological agents/drugs and gynecomastia

Elevated estrogen levels or Increase of its effects

- Systemic use or topical estrogen application (creams, cosmetics): isoflavones, phytoestrogens (cosmetics, soy products, beer, tea tree oil, lavender oil)
- Conversion of androgens to estrogens: excessive use of androgens (bodybuilding), anabolic substances, androgen-containing contraceptives, HCG-containing products
- Estrogen-like effects: diethylstilbestrol, clomifene, phenytoin, digitalis

Pharmacological agents/drugs and gynecomastia (2)

Decrease in androgen levels or its effects

- Inhibition of androgen synthesis: ketoconazole, metronidazole, GnRH agonists (chronic) and antagonists, spironolactone, cytotoxic chemotherapeutic agents
- Inhibition of testosterone effects: androgen receptor blockers (bicalutamide, flutamide, nilutamide, spironolactone, eplerenone, cyproterone (5-alpha reductase inhibitor: finasteride, dutasteride), H2 blockers (cimetidine, ranitidine), proton pump inhibitors, marijuana

Pharmacological agents/drugs and gynecomastia (3)

Multifactorial

- ACE inhibitors (angiotensin-converting enzyme inhibitors), alcohol, amiloride, amphetamine, calcium channel blockers, cyclosporine, diazepam, HAART (highly active antiretroviral therapy), heroin, methyldopa, isoniazid, reserpine, risperidone, theophylline, tricyclic antidepressants (through an increase in prolactin levels), growth hormone

Diagnostic workup of patients with gynecomastia

History	Beginning, course, symptoms, comorbidities, medication, alcohol, drugs. In case of suspected breast cancer: familial cancer, evidence of estrogen excess, radiation exposure
Clinical findings	General health, local clinical findings, accessory/ectopic breast tissue, andrological status, testicular palpation, lymph node status

Diagnostic workup of patients with gynecomastia (2)

Laboratory workup	Basic tests: T, E_2, LH, HCG, Additional tests: SHBG, PRL, FSH, TSH, fT_3, fT_4 DHEA, liver and kidney function tests, AFP, chromosome analysis
Imaging studies	Basic diagnostic tests: breast ultrasound, testicular ultrasound Additional diagnostic tests: mammogram, chest X-ray, MRI of the pituitary gland, ultrasound/CT of the abdomen
Special diagnostic tests	Histological workup in case of suspected neoplasm, tumor staging

Diagnostic algorithm in gynecomastia

	Clinical constellation	Basic workup
Typical	Adolescence	▸ Clinical examination ▸ Palpation of breasts and testicles ▸ T, E2, LH, HCG, ▸ Testicular ultrasound ▸ Clinical follow-up
	Senium	▸ Clinical examination ▸ Palpation of breasts and testicles ▸ T, E2, LH, HCG, ▸ Testicular ultrasound ▸ Follow-up ▸ Possibly testosterone
Atypical	For example, recent onset, unilateral, signs of hypogonadism	▸ Clinical examination ▸ Palpation of breasts and testicles ▸ Testicular ultrasound ▸ Breast ultrasound ▸ T, E2, LH, HCG, *Depending on the suspicion* ▸ Additional imaging studies and laboratory workup according to Table 5

Pharmacological treatment of gynecomastia

Active ingredient	Trial design	a)Results
Tamoxifen	Randomized, double-blind, placebo-controlled trial of ten patients (Parker et al. 1986)	Seven partial remissions on tamoxifen; none on placebo No significant therapeutic success
	Randomized, double-blind, placebo-controlled trial of six patients (McDermott et al. 1990)	Evidence of effectiveness and safety
	Several uncontrolled trials (Ting et al. 2000, Alagaratnam 1987, Khan et al. 2004, König et al. 1987, Eversmann et al. 1984, Derman et al. 2008)	
Clomifene	Prospective, uncontrolled trial, 19 patients (Stepanas et al. 1977)	Significant regression in eight patients; moderate regression in five patients
	Prospective, uncontrolled trial, 28 patients (Le Roith et al. 1980)	Regression in 14 of 22 evaluable patients
	Prospective, uncontrolled trial, 12 patients (Plourde et al. 1983)	Regression > 20 % in five patients

Pharmacological treatment of gynecomastia (2)

Danazol	Randomized, double-blind, placebo-controlled trial of 55 patients (Jones et al. 1990)	Significantly more effective than placebo; minor effects, though
	Several uncontrolled trials (Ting et al. 2000, Buckle 1979, Beck et al. 1982)	Evidence of effectiveness and safety
Dihydrotestosterone (topical)	Prospective, uncontrolled trial, four patients (Eberle et al. 1986)	Complete regression in ten patients; partial regression in 19 patients; and none, in 11 patients.
	Prospective, uncontrolled trial, 40 patients (Kuhn et al. 1983)	Partial regression in all patients
Testolactone	Prospective, uncontrolled trial, 22 patients (Zachmann et al. 1986)	Significant regression
	Prospective, uncontrolled trial, four patients (Braunstein and Glassman 1997)	Significant regression; complete regression in one case
Anastrozole	Case report of two patients on testosterone replacement therapy (Rhoden and Morgentaler 2004)	Regression following discontinuation of replacement therapy; no recurrence following reintroduction of said therapy in combination with anastrozole
	Prospective, uncontrolled trial, 42 patients, age 13 ± 1.8 years (Mauras et al. 2009)	Regression of area and volume by around 60 %

Appendix 2

Effect of BMI on Testosterone, SHBG, & Estradiol

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Daniela et al. Psychoneuroendocrinology 87 (2018) 196–203

Patients and Methods

- Data included to this study were obtained from the LIFE-Adult-Study, a population-based cohort study with more than 10,000 randomly selected deeply phenotyped adults aged 40–79 years
- **3925 men** were included into statistical analyses
- Anthropometric measurements were taken by trained study nurses according to standardized protocols
- The level of depressive symptomatology was assessed using a self-report questionnaire, the updated German version of the Center for Epidemiological Studies Depression Scale (CES-D)

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Patients and Methods

- Participants of the study were asked about medical diagnoses previously confirmed by a physician
- The interview contained more than 70 common diagnoses, including hormonal and mental disorders. Data on all medications taken within seven days prior to the interview were gathered
- Socioeconomic status was obtained in a structured interview and was calculated from information on education, occupational status and equivalent household income

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Results: Association between BMI and sex hormone binding globulin

- After exclusions, 2244 men<60 years old (47.6 ± 8.0 years) were included into analyses
- In the study group,
  - 34.5% were normal weight (mean BMI 23.1 ± 1.5 kg/m2),
  - 44.8% were overweight (mean BMI 27.1 ± 1.3 kg/m2) and
  - 20.6% were obese (mean BMI 33.5 ± 3.6 kg/m2)
- The **sex hormone-binding globulin** was significantly decreased in overweight (35.4 ± 14.1 nmol/L, p < 0.001) and obese men (31.8 ± 14.3 nmol/L, p< 0.001) compared to normal weight men (43.5 ± 16.0 nmol/L).

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Results: Association between BMI and total and free testosterone

- A significant decrease in **total testosterone** level in overweight (15.8 ± 5.2 nmol/L, $p < 0.001$) and obese men (12.6 ± 4.7 nmol/L, $p < 0.001$) compared to the normal weight individuals (19.4 ± 5.5 nmol/L) was observed
- **Free testosterone** level was significantly decreased in overweight (300.8 ± 78.6 nmol/L, $p < 0.001$) and in obese males (249.0 ± 73.9 mol/L, $p < 0.001$) compared to normal weight (337.2 ± 82.0)

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Results: Association between BMI and estradiol

- An increased **estradiol** level in obese (89.2 ± 39.5 pmol/L) compared to normal weight men (84.9 ± 36.7 pmol/L) was observed, although only with a borderline significance ($p = 0.072$). Higher estradiol/testosterone ratio was found in overweight (5.7 ± 4.5, $p < 0.001$) and obese (7.8 ± 4.4, $p < 0.001$) men compared to the normal weight men (84.9 ± 36.7) (Figure in next slide).

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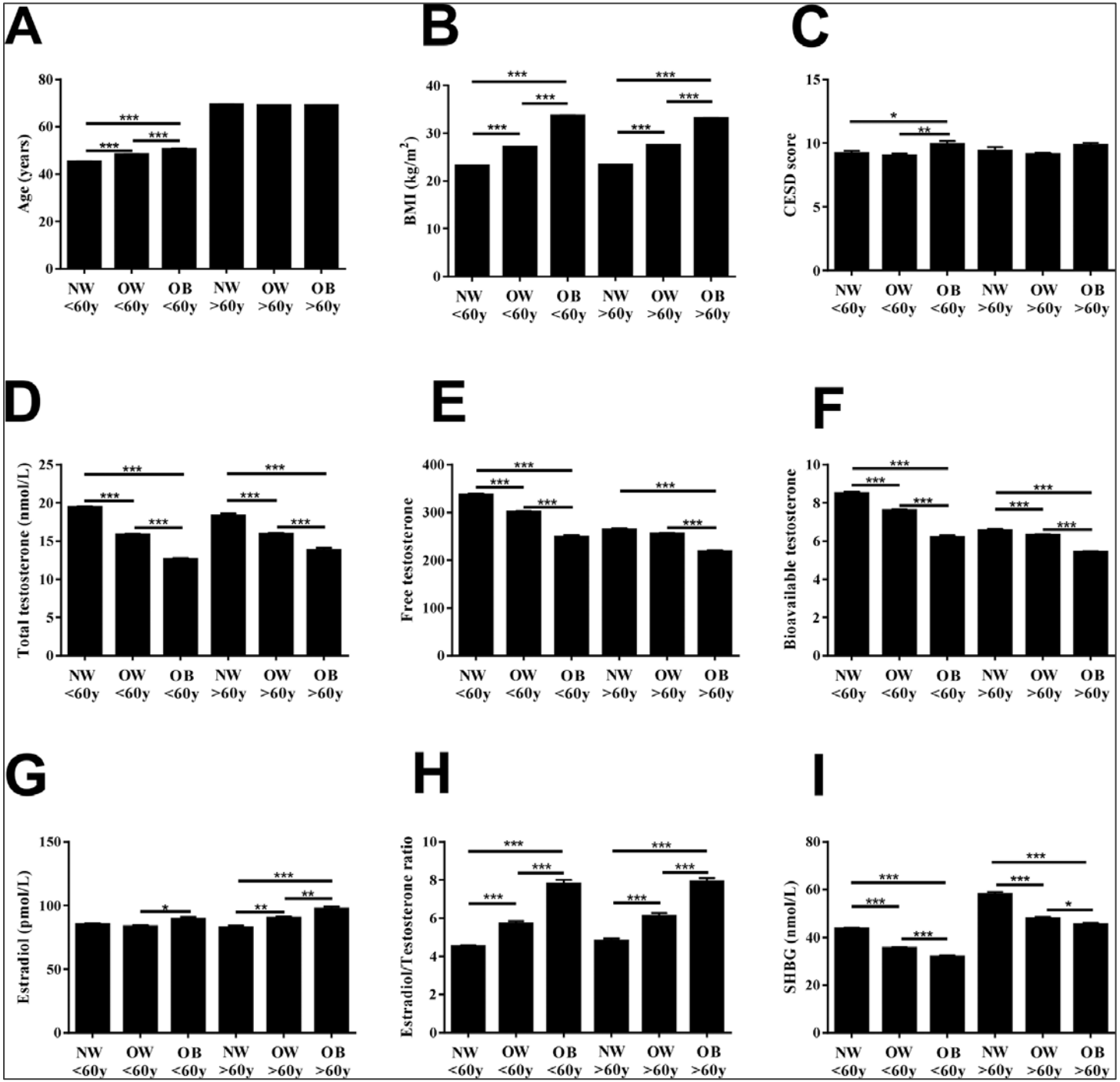

Sex hormone levels in men up to 60 years and over 60 years according to specific weight categories. Differences in the groups were calculated by t-test. Abbreviations: NW (normal weight), OW (overweight), OB (obese). Significant differences ($p \leq 0.05$) are marked with *, <0.01 with **, and <0.001 with ***.

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Results: Association between depressive symptomatology and sex hormones

- **Men <60 years old with depressive symptomatology had** (compared to men without depressive symptomatology) **higher estradiol level** (96.3 ± 40.7 vs 84.4 ± 36.6 pmol/L, p = 0.016).
- **In >60 years old men, no significant differences** in sex hormone levels in men with depressive symptomatology compared to men without depressive symptomatology were observed.
- **No significant differences in levels of total, free or bioavailable testosterone** were found in men with depressive symptomatology compared to men without depressive symptomatology

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Results: Association between symptomatology, BMI and sex hormones

- In<60 years old men was CES-D significantly higher in obese compared to normal weight men, but the mean score difference was small (9.9 ± 6.0 vs. 9.2 ± 5.8, p = 0.031) . No significant differences in the prevalence of depressive symptomatology (CESD > 23 points) in overweight (2.8%, p = 0.773) or obese (4.4%, p = 0.306) compared to normal weight (3.1%) men were observed.
- **Men with depressive symptomatology did not significantly differ in BMI** and waist circumference from those without depressive symptomatology

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Discussion

- We have shown that overweight and obese men have significant differences in serum sex hormone levels compared to normal weight individuals, and that BMI is the strongest predictor for these variations.
- We have also observed several hormonal differences between younger (< 60 years old) and older (> 60 years old) men, particularly in levels of free testosterone, bioavailable testosterone and estradiol with increasing BMI.
- Depressive symptomatology in younger men was significantly associated with higher estradiol levels; however, we did not find an association with increased BMI in them. No association between depressive symptomatology and BMI or sex hormones was found in older men in our study.

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Conclusion

- This is one of the first studies to show an association between higher estradiol levels and depression in younger men.
- Nevertheless, we did not confirm that this is directly associated with increased BMI in men, a condition also associated with altered sex hormone levels.
- As the prevalence of depression and obesity is increasing, there is an urgent need to elucidate the role of estrogens and BMI in the mechanism of depression in males.
- To this aim, studies of severely obese younger men would be of particular importance, as they are specially vulnerable to hormonal changes and depression.

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Appendix 3
Estrogens in Men: Clinical Implications for Sexual Function and the Treatment of Testosterone

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This information is not a recommendation nor is it intended to provide direction regarding diagnoses, treatments, or potential outcomes. Any interpretation of this information is the opinion of Clinic Optimizers and should be used by the prescriber at his/her discretion.

Ravi Kacker, MD, Abdulmaged M. Traish, PhD, and Abraham Morgentaler, MD. J Sex Med. 2012 Jun;9(6):1681-96.

Abstract

- ***Results***

- Estradiol elicits a variety of physiological responses in men and may contribute to modulation of sexual function.
- In the absence of testosterone deficiency, elevations in estrogens do not appear to be harmful and estrogens may help maintain some, but not all, sexual function in castrated men.
- While the therapeutic use of estrogens at pharmacologic doses has been used to suppress serum testosterone, naturally occurring elevations of estrogens do not appear to be a cause of low testosterone.
- During testosterone replacement, estrogens may rise and occasionally reach elevated levels. There is a lack of evidence that treatment of elevated estrogen levels during testosterone replacement has benefit in terms of male sexuality.
- ***Conclusion*** Further research on the importance of estrogens in male sexual function is needed. Current evidence does not support a role of naturally occurring estrogen elevations in testosterone deficiency or the treatment of elevated estrogens during testosterone therapy

Estrogens- Isoflavones and SERMS

- Nonsteroidal compounds such as isoflavones are sometimes classified as “phytoestrogens” as they are found in a variety of plants, notably soy. These compounds have a spatial relationship between hydroxyl groups similar to those found in E2 and can bind ERb, although only at one-third of the affinity [*].
- Equol, a metabolite of soy isoflavones, can also bind ERa. However, the bacteria required to produce equol are not universally present in human flora and circulating serum concentrations are low even when these bacteria are present [**].
- Isoflavones may also act as E2 agonists on cell membrane receptors and lead to rapid ER independent effects [***].
- Pharmaceuticals such as clomiphene citrate and tamoxifen are classified as selective ER modulators (SERMs). These compounds bind to both ERa and ERb and have agonist and antagonistic activity specific to target tissues.

[*] Molla MDJ, Hidalgo-Mora JJ, Soteras MG. Phytotherapy as alternative to hormone replacement therapy. Front Biosci 2011;S3:191–204
[**] Messina M. Soybean isoflavone exposure does not have feminizing effects on men: A critical examination of the clinical evidence. Fertil Steril 2010;97:2095–104
[***] Ricketts ML, Moore DD, Banz WJ, Mezei O, Shay NF. Molecular mechanisms of action of the soy isoflavones includes activation of promiscuous nuclear receptors. A review. J Nutr Biochem 2005;16:321–30

Epidemiology of Estrogens in Men

- Compared with T, E2 is an approximately 200-fold more potent inhibitor of gonadotropins (LH and FSH) [*].
- As T is the substrate for approximately 80% of serum E2
- It should be noted that most clinical studies have used commercially available immunoassays, which may have limited precision and accuracy for measurement of lower E2 levels compared to newer LC/MS assays [**].

[*] Finkelstein JS, O'Dea LS, Whitcomb RW, Crowley WF. Sex steroid control of gonadotropin secretion in the human male II effects of estradiol administration in normal and gonadotropin-releasing hormone-deficient men. J Clin Endocrinol Metab 1991;73:621–8
[**] Middle JG, Kane JW. Oestradiol assays: Fitness for purpose? Ann Clin Biochem 2009;46:441–56.

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Estradiol and Age

- Some studies have shown an age-related decrease in bioavailable E2 with age, but not total serum E2 [*,**].
- Longitudinal data on E2 are lacking, but serum E1 decreased by 3.6% per year over 7–10 years for men enrolled in the Massachusetts Male Aging Study (MMAS).
- A greater decrease in T compared with E2 with age was reported in all cross-sectional studies reviewed, leading to a decreased T : E2 ratio with age

[*] Vermeulen A, Kaufman JM, Goemaere S, van Pottelberg I. Estradiol in elderly men. Aging Male 2002;5:98–102
[**] Khosla S, Melton J, Atkinson EJ, O'Fallon WM. Relationship of serum sex steroid levels to longitudinal changes in bone density in young versus elderly men. J Clin Endocrinol Metab 2001;86:3555–61

Estradiol and Body Mass Index (BMI)

- Obese men have a direct relationship between E2 and BMI [*, **].
- These findings are not universal, however, and in the MrOS study, BMI did not influence the age-related decrease in E2 although a weak relationship with free E2 was observed [***].
- These different results may be due to the fact that BMI reflects both visceral fat, with low aromatase activity, and subcutaneous and gluteal fat with a 10-fold higher aromatase activity.

[*] Vermeulen A, Kaufman JM, Goemaere S, van Pottelberg I. Estradiol in elderly men. Aging Male 2002;5:98–102
[**] Muller M, den Tonkelaar I, Thijssen JH, Grobbee DE, van der Schouw YT. Endogenous sex hormones in men aged 40–80 years. Eur J Endocrinol 2003;149:583–9
[***] Middle JG, Kane JW. Oestradiol assays: Fitness for purpose? Ann Clin Biochem 2009;46:441–56.

Men's Estradiol and Race

- A large multinational study of sex steroid levels in 5,003 men reported 10–16% higher E2 levels in African and African-American men compared with Asian and Caucasian men independent of age, BMI, and geography.
- E2 : T ratios were also higher, suggesting that increased aromatase activity may mediate racial differences in sex-hormone levels [*].
- Interestingly, African-American men have a lower rate of hip fractures, for which low E2 may be a risk factor [**].

[*] Orwoll ES, Nielson CM, Labrie F, Barrett-Connor E, Cauley JA, Cummings SR, Ensrud K, Karlsson M, Lau E, Leung PC, Lunggren O, Mellström D, Patrick AL, Stefanick ML, Nakamura K, Yoshimura N, Zmuda J, Vandenput L, Ohlsson C; Osteoporotic Fractures in Men (MrOS) Research Group. Evidence for geographical and racial variation in serum sex steroid levels in older men. J Clin Endocrinol Metab 2010;95:E151–60
[**] Baron JA, Barrett J, Malenka D, Fischer E, Kniffin SW, Bubolz T, Tosteson T. Racial difference in fracture risk. Epidemiology 1994;5:42–7

Role of Estrogen in Men: Bone

- Longitudinal studies have shown that low total and bioavailable E2 levels are associated with increased rate of bone loss, with increased risk at a threshold of 40 pmol/L [*].
- Androgen deprivation therapy with GnRH agonists for prostate cancer, which leads to dramatic reductions in both T and E2, leads to a decrease in bone mineral density of up to 13% annually and an increased risk of fracture [**].

[*] Khosla S, Melton J, Atkinson EJ, O'Fallon WM. Relationship of serum sex steroid levels to longitudinal changes in bone density in young versus elderly men. J Clin Endocrinol Metab 2001;86:3555–61
[**] Guise TA, Oefelein MG, Eastham JA, Cookson MS, Higano CS, Smith MR. Estrogenic side effects of androgen deprivation therapy. Rev Urol 2007;9:163–80

Role of Estrogen in Men: Bone and Cardiovascular System

- For one man with aromatase deficiency, treatment with T and E2, but not T alone, increased cortical thickness and normalized bone turnover parameters [*]. Estrogen appears to be necessary for normal bone development, but T may also appear to have independent effects through androgen receptors (ARs) on radial bone growth [**].
- T and E2 together may facilitate endothelial-dependent vasodilation [***] and prevent atherogenesis [****].

[*] Rochira V, Zirilli L, Madeo B, Aranda C, Caffagni G, Fabre B, Montangero VE, Roldan EJ, Maffei L, Carani C. Skeletaleffects of long-term estrogen and testosterone replacement in a man with congenital aromatase deficiency evidences of a priming effect of estrogen for sex steroids action on bone. Bone 2007;40:1662–8
[**] Clarke BL, Khosla S. Androgens and bone. Steroids 2009;74: 296–305.
[***] Sader MA, Celermajer DS. Endothelial function, vascular reactivity and gender differences in the cardiovascular system. Cardiovasc Res 2002;53:597–604.
[****] Pottelbergh IV, Braeckman L, De Bacquer DD, De Backer G, Kaufman JM. Differential contribution of testosterone and estradiol in the determination of cholesterol and lipoportein profile in healthy middle-aged men. Atherosclerosis 2003;166:95–102

Role of Estrogen in Men- Lipids and Prostate Cancer

- A balance between T and E2 may regulate lipid accumulation and glucose homeostasis. Further study is needed, but excess T in the absence of E2 could potentially be harmful.
- The importance of estrogens in prostate health is a hotly debated topic, with some studies showing changes in ER distribution in high grade prostate cancer [*].
- Treatment with estradiol in men with prostate cancer undergoing testosterone blockage improved mood and bone density. No accelerated progression was seen.

[*] Bonkoff H, Berges R. The evolving role of oestrogens and their receptors in the development and progression of prostate cancer. Eur Urol 2009;55:533–42

Estradiol and Male Sexual Development

- A 28-year-old male with loss-of-function mutation in the ERa, normal total T, and elevated E2 reported strong heterosexual interest and normal erectile and ejaculatory function [*].
- In another case, a 27-year-old male with congenital aromatase deficiency leading to undetectable E2 and low but detectable E1 also had normal pubertal development and erections sufficient for penetration.

[*] Smith EP, Boyd J, Frank GR, Takahashi H, Cohen RM, Specker B, Williams TC, Lubahn DB, Korach KS. Estrogen resistance caused by a mutation in the estrogen-receptor gene in a man. N Engl J Med 1994;331:1056–61

Estradiol and Male Sexual Function

- In humans, population-based and cohort studies have not shown a relationship between estrogen levels and sexual function. It is possible that estrogenic sexual effects are different for eugonadal (normal T), hypogonadal (low T), and castrated men. For castrated men, there is some evidence that estrogens may maintain some sexual function in the absence of T

[*] Bonkoff H, Berges R. The evolving role of oestrogens and their receptors in the development and progression of prostate cancer. Eur Urol 2009;55:533–42

Estradiol and Male Sexual Function (2)

- Libido and erectile function were assessed by the Brief Male Sexual Function Inventory and **no correlation with serum E2 was found** [*]. Similarly, a cohort study of 348 men hospitalized with urologic or musculoskeletal problems found no relationship between E2 levels and International Index of Erectile Function (IIEF) scores.
- However, increased E2, but not decreased T, was associated with nonsexual symptoms on the [**].
- Another cohort study of 375 healthy men aged 45–85 years found that E2 levels correlated with T but not with sexual or nonsexual AMS scores [***]

[*] Gades NM, Jacobson DJ, McGree ME, St Sauver JL, Lieber MM, Nehra A, Girman CJ, Klee GG, Jacobsen SJ. The associations between serum sex hormones, erectile function, and sex drive: The Olmsted County Study of urinary symptoms and health status among men. J Sex Med 2008;5:2209–20.
[**] Basar MM, Aydin G, Mert HC, Keles I, Caglayan O, Orkun S, Batislam E. Relationship between serum sex steroids and aging male symptoms score and International Index of Erectile Function. Urology 2005;66:597–601
[***] Ponholzer A, Plas E, Schatzl G, Jungwirth A, Madersbacher S. Association of DHEA-S and estradiol serum levels to symptoms of aging men. Aging Male 2002;5:233–8

Estradiol and Male Sexual Function (2)

- While cohort and population-based studies have not demonstrated a relationship between ED and E2, **E2 may be implicated in the subset of men with ED secondary to venous leakage**. A comparison of men with cavernosal veno-occlusive dysfunction had significantly higher E2 levels compared with patients with ED due to other causes [*].
- **E2 has been found to accelerate repair of arterial injury** through induction of nitric oxide and vascular endothelial growth factor (VEGF) expression [**], and one may speculate that a related vascular mechanism may play a role in men with ED

[*] Mancini A, Milardi D, Bianchi A, Summaria V, De Marinis L. Increased estradiol levels in venous occlusive disorder: A possible functional mechanism of venous leakage. Int J Impot Res 2005;17:239–42
[**] Chambliss KL, Shaul PW. Estrogen modulation of endothelial nitric oxide synthase. Endocr Rev 2002;23:665–86.

Estradiol and Male Sexual Function (3)

- Several investigators and clinicians have hypothesized that the interactions between androgens and estrogens, possibly reflected in the **T : E2 ratio, may be important to sexual function.**
- However, direct evidence of the importance of this ratio is limited. A study of men with ED showed an increase in the T : E2 ratio after 12 months of successful treatment with tadalafil. This was primarily driven by decreases in E2 and was observed in nonobese patients only [*]

[*] Greco EA, Pili M, Bruzziches R, Corona G, Spera G, Aversa A. Testosterone: Estradiol ratio changes associated with longterm tadalafil administration: A pilot study. J Sex Med 2006;3: 716–22

Estradiol in Chemically or Physically Castrated Men

- Studies of castrated men suggest that **E2 may play a role with respect to erectile function but may be less important for libido.**
- Some data come from men undergoing hormonal therapy with estrogen for prostate cancer and from individuals undergoing male-to-female (MtF) gender reassignment.
- Men undergoing castration surgically or using a GnRH analog may also yield insight into the role of estrogens. Castration produces profound decreases in both T and E2, but E2 decreases by a smaller amount. E1 may still be produced through aromatization of adrenally produced androstenedione, and some E1 may ultimately be converted to E2 [*]

[*] Vermeulen A, Kaufman JM, Goemaere S, van Pottelberg I. Estradiol in elderly men. Aging Male 2002;5:98–102

Estradiol and Gynecomastia in Castrated Men (2)

- Up to 10% of men with prostate cancer treated with orchiectomy (castration) and an even higher proportion treated with a gonadotropin release hormone GnRH analog (to block T) may develop gynecomastia. Tamoxifen, a SERM with antagonistic effects to breast tissue, is effective in reversing gynecomastia, providing further evidence for estrogenic activity in castrated men [*].

[*] Dobs A, Darkes MJM. Incidence and management of gynecomastia in men treated for prostate cancer. J Urol 2006;174: 1737–42.

Estradiol and Sexual Function in Castrated Men (3)

- A review of castration of European sex offenders in the early 20th century found that some men retained a capacity for sexual intercourse. A more modern German study of sex offenders in the 1970s used a control group of non-castrated sex offenders but still relied on self-reported sexual symptoms.
- One-third of men reported erections sufficient for penetration, but all men reported a decrease in libido. Only 5% reported a “less than profound” decrease in sexual interest [*].
- The question arises whether variation in nonandrogenic hormones, especially estrogens, may account for the persistence of sexual function and desire in some of these men.

[*] Weinberger LE, Sreenivasan S, Garrick T, Osran H. The impact of surgical castration on sexual recidivism risk among sexually violent predatory offenders. J Am Acad Psychiatry Law 2005;33:16–26

Estradiol and Sexual Function in Castrated Men (4)

- These data on castrated men come from small studies or historical anecdotes but suggest that estrogens may contribute to maintenance of sexual function in men in the absence of T.
- Men with prostate cancer treated with an AR antagonist such as bicalutamide are likely to have higher E2 levels through aromatization of T. Patients treated with an antiandrogen alone have a higher rate of gynecomastia compared with men treated with surgical castration [*].
- Bales and Chodak [**] and Tyrrell et al. [***] found greater quality of life secondary to sexual function and interest in prostate cancer patients randomized tobicalutamide compared with castration. These findings may result from the preservation of normal estrogen levels in men treated with an AR antagonist compared with the profoundly decreased estrogen levels seen in men who undergo castration

[*] Guise TA, Oefelein MG, Eastham JA, Cookson MS, Higano CS, Smith MR. Estrogenic side effects of androgen deprivation therapy. Rev Urol 2007;9:163–80
[**] Bales GT, Chodak GW. A controlled trial of bicalutamide versus castration in patients with advanced prostate cancer. Urology 1996;47:38–43
[***] Tyrrell CJ, Kaisary AV, Iversen P, Anderson JB, Baert L, Tammela T, Chamberlain M, Webster A, Blackedge G. A randomized comparison of "Casodex" (bicalutamide) 150 mg monotherapy versus castration in the treatment of metastatic and locally advanced prostate cancer. Eur Urol 1998;33:447– 56.

Estrogens in Male-to-Female Transgenders (5)

- Studies of sexual function in male-to female transwomen (MtFs) are limited by self-selection of estrogen supplementation and timing of gender reassignment surgery.
- However, this unique group provides some data on estrogen use in castrated genetic males.
- One study involved 25 presurgical MtFs receiving transdermal estrogen in addition to androgen suppression with an androgen antagonist, GnRH analogs, or both.
- All men reported no change in erectile function after hormonal therapy as assessed by the IIEF-15 questionnaire, although these data were not gathered prospectively. All men had normal penile color coded Doppler ultrasonography (CDU) during pharmacologic and self-stimulated erection and 12 of the 25 men had normal nocturnal penile tumescence (NPT) tests.
- Interestingly, NPT results were highly correlated with T levels, whereas there was no relationship between T and CDU measures.
- These data suggest that T may be required for nocturnal erections, but non-androgen pathways, possibly mediated by E2, may maintain sexually stimulated erection in the absence of T [*]. At our center, one MtF sought care for painful erections adequate for vaginal intercourse despite being on high-dose estrogens with presumably suppressed T

[*] Bettocchi C, Palumbo F, Cormio L, Ditonno P, Battaglia M, Selvaggi FP. The effects of androgen depletion on human erectile function: A prospective study in male-to-female transsexuals. Int J Impot Res 2004;16:544–6

Estradiol in Castrated Men (6)

- These historical accounts and studies of castrated men suggest that in the absence of T, **E2 may be sufficient for sexually stimulated erections but may not be sufficient for maintaining sexual interest and nocturnal erections**
- In contrast to animal studies suggesting a role for estrogen in facilitating mating behavior, there is **a lack of data on the influence of E2 on libido and sexual interest in men with low T**

Estradiol Blockage in Eugonadal (Normal T) Men

- Two studies have examined the role of estrogens in eugonadal men and suggest that aromatization of T is not required for normal sexual function. In a double-blinded randomized controlled trial, young healthy volunteers were administered a GnRH antagonist and then were randomized to receive T replacement with or without testolactone, an aromatase inhibitor.
- Men who received T replacement and testolactone had profoundly decreased E2 levels compared with men who did not receive testolactone. However**, there was no difference in the frequency of sexual fantasies, masturbation, and intercourse between men who had T replacement with and without testolactone** [*].
- Similarly, **Gooren did not find any change in sexual function after administering testolactone or tamoxifen to healthy, eugonadal men** [**].
- While these studies show that sexual function is not affected by acute withdrawal of estrogen in young, eugonadal men, **the effect of chronic inhibition of estrogenic activity is not known**

[*] Bagatell CJ, Heiman JR, Rivier JE, Bremner WJ. Effects of endogenous testosterone and estradiol on sexual behavior in normal young men. J Clin Endocrinol Metab 1994;78:711–6.
[**] Gooren LJ. Human male sexual functions do not require aromatization of testosterone: A study using tamoxifen, testolactone, and hihydrotestosterone. Arch Sex Behav 1985;14: 539–48.

Causes of Elevated Estradiol in Men: BMI and Race

- The upper limit of normal for E2 in men is not clinically defined. Laboratory reference ranges are assay dependent, but the upper bound is often stated as approximately **50 pg/mL or 160 pmol/L**.
- BMI and African descent may be correlated with higher levels of E2.
- Obesity is associated with an increase in E2 [*], likely secondary to increased aromatase activity in subcutaneous and gluteal fat [**].
- Interestingly, E2 was reduced in obese men 2 years after gastric bypass surgery, and SHBG was increased, resulting in an even greater decrease in bioavailable E2 [***].

[*] Vermeulen A, Kaufman JM, Goemaere S, van Pottelberg I. Estradiol in elderly men. Aging Male 2002;5:98–102.
[**] Vermeulen A, Goemaere S, Kaufman JM. Sex hormones, body composition and aging. Aging Male 1999;2:8–11.
[***] Hammoud A, Gibson M, Hunt S, Adams TD, Carrell DT, Kolotkin RL, Meikle AW. Effect of Roux-en-Y gastric bypass surgery on the sex steroids and quality of life in obese men. J Clin Endocrinol Metab 2009;94:1329–32.

Causes of Elevated Estradiol in Men: Genetics

- **Genetic differences in aromatase** may account for some of the difference in E2 levels in men. Homozygosity for a mutation in the CYP19 gene that codes for aromatase in young Swedish men results in 13% higher E2 compared with the normal genotype
- **Polymorphisms in the aromatase gene** may also be associated with an increased incidence of gynecomastia [*]. A rare gain-of-function mutation leading to increased aromatase activity by 11–24 times and markedly elevated E2 levels has also been identified

[*] Czajka-Oraniec I, Zgliczynski W, Kurylowicz A, Mikula M, Ostrowsi J. Association between gynecomastia and aromatase (CYP19) polymorphisms. Eur J Endocrinol 2008;158:721–7

Clinic Optimizers

Causes of Elevated Estradiol in Men (3)

- At least one man with this mutation presented with gynecomastia and hypogonadotropic hypogonadism [*]. It is conceivable that other gain-of-function mutations exist and may not be rare in some populations.
- Population-based studies have not found a conclusive relationship between alcohol consumption and T or E2 levels [26,30]
- **Antiepileptic drugs**, such as phenytoin and carbemazapime, are associated with high E2 levels in men with sexual dysfunction [****].

[*] Shozu M, Sebastian S, Takayama K, Hsu WT, Schultz RA, Neely K, Bryant M, Bulun SE. Estrogen excess associated with novel gain-of-function mutations affecting the aromatase gene. N Engl J Med 2003;348:1855–65

[**] Ferrini RL, Barrett-Connor E. Sex hormones and age: A cross-sectional study of testosterone and estradiol and their bioavailable fractions in community-dwelling men. Am J Epidemiol 1998;147:750–4

[***] Bjornerem A, Straume B, Midtby M, Fonnebo V, Sundsfjord J, Svartberg J, Acharya G, Oian P, Berntsen GK. Endogenous sex hormones in relation to age sex, lifestyle factors and chronic diseases in a general population: The Tromso study. J Clin Endocrinol Metab 2004;89:6039–47

[****] Murialdo G, Galimberti CA, Fonzi S, Manni R, Costelli P, Parodi C, Solinas GP, Amoretti G, Tartara A. Sex hormones and pituitary function in male epileptic patients with altered or normal sexuality. Epilepsia 1995;36:360–5

Elevated Estradiol and T Deficiency

- Low T is most often associated with reduced concentrations of E2, not elevated E2. In population-based studies, total T parallels total E2, even at lower T levels [*].
- A study of men undergoing TRT suggested a limited relationship between T and E2 levels in men. No difference in E2 was found between men with very low (<200 ng/dL), low (200–300 ng/dL), or "normal" (>300 ng/dL) serum T [**].
- Although the data indicate that the majority of T-deficient men have low or normal levels of E2, some of these men will have elevated E2. It remains to be determined whether these men respond differently to TRT compared with men without elevated E2. In addition, it appears to be unknown whether reducing serum E2 provides additional benefits to these men. While E2 is measured in many studies of TRT (Table in next slide), they did not identify any studies that examined the relationship between E2 and response to TRT. This is a topic that merits investigation

[*] Orwoll E, Lambert L, Marshall LM, Phipps K, Blank J, Barrett-Connor E, Cauley J, Ensrud K, Cummings S. Testosterone and estradiol among older men. J Clin Endocrinol Metab 2006;91:1336–44
[**] Reyes-Vallejo L, Lazarou S, Morgentaler A. Subjective sexual response to testosterone replacement therapy based on initial serum levels of total testosterone. J Sex Med 2007;4:1757–62

Aromatase Inhibitors in T Deficient Men: Anastrozole and Letrozole

- Men with normal T have increases in LH and T in response to anastrozole [*]. Similarly, aromatase inhibitors increase T levels and decrease E2 levels in men with low T. E2 is known to suppress gonadotropins and some of the increase in T is likely due to reduced negative feedback from E2. T may also rise from decreased peripheral conversion to E2.
- Only two studies of aromatase inhibitors in men with low T were identified in this review. A study of letrozole in severely obese men with hypogonadism demonstrated a significant increase in LH and T and decrease in E2 from baseline. T levels increased by 6 weeks and were sustained after 6 months of treatment. The presence of symptoms of low T at baseline and the response to letrozolewas not reported [**]

[*] Hayes FJ, Seminara SB, Decruz S, Boepple PA, Aromatase CWF. Inhibition in the human male reveals a hypothalamic site of estrogen feedback. J Clin Endocrinol Metab 2000;85: 3027–35
[**] Loves S, Ruinemans-Koert J, de Boer H. Letrozole once a week normalizes serum testosterone in obesity-related male hypogonadism. Eur J Endocrinol 2008;158:741–7.

Anastrozole monotherapy increased T but did not improve symptoms in men with low T

- In another study, 88 men with low T over 60 years were randomized to anastrozole or placebo.
- At baseline, all men reported symptoms of low T as determined by the Androgen Deficiency in Aging Males (ADAM) questionnaire.
- For men treated with anastrozole, T levels peaked after 3 months and were still significantly increased over baseline and placebo at 12 months.
- After 12 months of treatment, 11 of 44 patients receiving a placebo reported resolution of symptoms of low T, compared with only seven of 44 patients receiving anastrozole. Furthermore, patients treated with anastrozole did not have changes in body composition or muscle strength, or an increase in hematocrit, as would normally be seen in TRT studies [*].
- It is worth noting that in this one study sexual symptoms were not improved despite normalization of serum T

[*] Burnett-Bowie AM, Roupeniean KC, Dere M, Lee H, Leder B. Effects of aromatase inhibition in hypogonadal older men: A randomized, double-blind, placebo controlled trial. Clin Endocrinol (Oxf) 2009;70:116–23..

Aromatase Inhibitors in T Deficient Men

- These results should be interpreted with caution given concerns regarding accuracy of the assays used [*]. However, elevated E2 does not appear to be common in these men with low T.
- In these two studies, aromatase inhibitors alone did not relieve symptoms of low T despite normalizing T levels.
- However, it is also possible that aromatization of T to E2 is partially responsible for some of the symptomatic and body composition response. Further research on the use of aromatase inhibitors in men with low T is needed.

[*] Middle JG, Kane JW. Oestradiol assays: Fitness for purpose? Ann Clin Biochem 2009;46:441–56..

Clinic Optimizers

Selective Estrogen Modulators (SERM) in T Deficient Men

- Clomiphene citrate is a SERM sometimes used in the treatment of T deficiency, particularly when maintenance of fertility is desired, as treatment does not reduce gonadotropins or sperm concentration. Clomiphene acts as a weak estrogen antagonist at the level of the hypothalamus [*], increasing GnRH pulse frequency and both LH and follicle-stimulating hormone [**].
- Shabsigh et al. treated 36 men with T deficiency with clomiphene citrate for 4–6 weeks and observed increases of nearly 150% in serum T [***]. Other studies have shown improvement in erectile function with clomiphene citrate in men with secondary T deficiency [****] and a recent nonrandomized study showed similar improvement in ADAM scores with clomiphene citrate compared with topical TRT [*****].

[*] Goldstein SR, Siddhanti S, Ciaccia AV, Plouffe L. A pharmacological review of selective oestrogen receptor modulators. Hum Reprod Update 2000;6:212–4
[**] Tan RS, Vasudevan D. Use of clomiphene citrate to reverse premature andropause secondary to steroid abuse. Fertil Steril 2003;79:203–5
[***] Shabsigh A, Kang Y, Shabsigh R, Gonzalez M, Liberson G, Fisch H, Goluboff E. Clomiphene citrate effects on testosterone/estrogen ratio in male hypogonadism. J Sex Med 2005;2:716–21
[****] Guay AT, Bansal S, Heatley GJ. Effect of raising endogenous testosterone levels in impotent men with secondary hypogonadism. Double blind placebo-controlled trial with clomiphene citrate. J Clin Endocrinol Metab 1995;80:3546–52.
[*****] Taylor F, Levine L. Clomiphene citrate and testosterone gel replacement therapy for male hypogonadism: Efficacy and treatment cost. J Sex Med 2010;7:269–76

Estrogen Modulators in T Deficient Men (2)

- While clomiphene citrate likely works by decreasing negative estrogenic feedback on the HPG axis, symptomatic benefit may be primarily due to increases in T alone. In the study by Shabsigh et al., T : E2 ratios increased, but this was driven by increases in T. Average E2 was not elevated at baseline and there was a nonsignificant increase from 32.3 to 46.3 pg/mL after treatment with clomiphene
- Tamoxifen has also been shown to raise T levels and may be effective in the treatment of male infertility [*] but does not seem to affect sexual function in healthy young men [**]. Further research is needed to determine how peripheral estrogenic effects of SERMs relate to male sexual function in the setting of T deficiency

[*] Kadioglu TC. Oral tamoxifen citrate treatment is more effective in normogonadotropic patients who have folliclestimulating hormone levels within the lower half of normal. Int Urol Nephrol 2009;41:773–6
[**] Gooren LJ. Human male sexual functions do not require aromatization of testosterone: A study using tamoxifen, testolactone, and hihydrotestosterone. Arch Sex Behav 1985;14: 539–48

Estrogen Response to TRT

- The response of estrogen to T administration was studied by Lakshman et al. In a group of young men and another group of older men, T enanthate was administered after pharmacologic gonadotropin suppression with leuprolide. Both total and free E2 levels increased with T administration in a dose-dependent fashion that was consistent with saturable Michaelis-Menten kinetics. There was a higher rate of aromatization in the group of older men that was partially but not completely explained by greater fat mass [*].
- These results suggest that in T-deficient men, TRT should result in an increase in serum E2, possibly with greater increases in older or obese men.

[*] Lakshman KM, Kaplan B, Travison TG, Basarla S, Knapp PE, Singh AB, LaValley MP, Manzer NA, Bhasin S. The effects of injected testosterone dose and age on the conversion of testosterone to estradiol and dihydrotestosterone in young and older men. J Clin Endocrinol Metab 2010;95: 3955–64.

Estrogen Response to TRT (2)

- The increases in E2 paralleled increases in T, which is in accordance with the results shown by Lakshman et al. Additionally, there was an overall trend to greater increases with T injections, compared with topical therapies, although this was not rigorously evaluated. This may be due to higher peak serum T concentrations. Intramuscular T undecanoate may lead to greater increase in E2 over T enanthate [*].
- In these studies, the number of patients who developed E2 levels above the normal range was not reported, however mean values were all well within normal limits. Interestingly, in some cases, an initial elevation in E2 was followed by decreased E2 after prolonged TRT [**].
- This may be due to reduced adipose mass or decreased T concentrations. This observation was also seen in the study by Schubert et al. in which 14 of 32 patients treated for 28 months with intramuscular T undecanoate demonstrated an initial increase inE2 followed by a subsequent decline [*]

[*] Schubert M, Minnemann T, Hubler D, Rouskova D, Christoph A, Oettel M, Ernst M, Mellinger U, Krone W, Jockenhovel F. Intramuscular testosterone undecanoate: Pharmacokinetic aspects of a novel testosterone formulation during long-term treatment of men with hypogonadism. J Clin Endocrinol Metab 2004;89:5429–34

[**] Amory JK, Watts NB, Easley KA, Sutton PR, Anawalt BD, Matsumoto AM, Bremmer J, Tenover JL. Exogenous testosterone with finasteride increases bone mineral density in older men with low serum testosterone. J Clin EndocrinolMetab 2004;89:503–10.

Estrogen Response to TRT (3)

- Amory et al. studied patients receiving T enanthate with or without inasteride. The authors found that E2 increased after therapy in both groups, with greater E2 increases for patients receiving finasteride
- Inhibition of the conversion of T to DHT may result in increased availability of T as a substrate for aromatization to E2. DHT is not aromatizable but may be converted to an estrogen, 3bD, though aromatase-independent pathways. Compared with E2, 3bD is a weak binder of the ER and its clinical relevance is unknown [*]. It is possible that five alpha reductase inhibitors may increase estrogenic activity in men, as suggested by the occasional development of gynecomastia in men receiving these medications

[*] Ishikawa T, Glidewell-Kenny C, Jameson JL. Aromataseindependent testosterone conversion into estrogenic steroids is inhibited by a 5a-reductase inhibitor. J Steroid Biochem Mol Biol 2006;98:133–8

Elevated E2 During TRT: To Treat or Not To Treat?

- TRT may lead to elevations in serum E2 and in some cases to levels above the upper limit of normal. The development of nipple or breast tenderness or frank gynecomastia has been reported in association with TRT, and in these cases there is a clear indication for the use of aromatase inhibitors to reduce E2. Some authors recommend withdrawal first of TRT with subsequent resolution of symptoms, followed by the use of aromatase inhibitors together with reinitiation of TRT [*].
- Some clinicians, particularly in the antiaging community, advocate the routine use of aromatase inhibitors with TRT even in the absence of symptoms of estrogen excess. These clinicians believe that maintaining a relatively low estrogen concentration improves male health and the efficacy of TRT

[*] Rhoden EL, Morgentaler A. Treatment of testosteroneinduced gynecomastia with the aromatase inhibitor, anastrozole. Int J Impot Res 2004;16:95–7

Clinic Optimizers

Elevated E2 During TRT: To Treat or Not To Treat? (2)

- However, the basis for this belief is uncertain. In one randomized controlled trial, treatment of men with low T with anastrozole normalized T levels, but there was no improvement in symptoms of low T or changes in body composition, muscle strength, or hematocrit [*]. Further studies of this nature are needed. Furthermore, E2 levels in some men treated with aromatase inhibitors decreased below 40 pmol/L, considered the threshold at which there is increased risk of developing osteoporotic changes.
- Additionally, case reports of men with congenital aromatase deficiency suggest that aromatase inhibition may risk decreasing insulin sensitivity, potentially worsened by TRT [44,45]

[*] Burnett-Bowie AM, Roupenian KC, Dere M, Lee H, Leder B. Effects of aromatase inhibition in hypogonadal older men: A randomized, double-blind, placebo controlled trial. Clin Endocrinol (Oxf) 2009;70:116–23
[**] Maffei L, Murata Y, Rochira V, Tubert G, Aranda C, Vazquez M, Clyne CD, Davis S, Simpson ER, Carani C. Dysmetabolic syndrome in a man with a novel mutation of the aromatase gene: Effects of testosterone, alendronate, and estradiol treatment. J Clin Endocrinol Metab 2004;89:61–70
[***] Rochira V, Madeo B, Zirilli L, Caffagni G, Maffei L, Carani C. Oestrasiol replacement treatment and glucose homeostasis in two men with congenital aromatase deficiency: Evidence for a role of oestradiol and sex steroids imbalance on insulin sensitivity in men. Diabet Med 2007;24:1491–5.

Does Adding Anastrozole or Testolactone Improve Libido in Men on TRT with High E2?

- The only trials identified in this review that compared the use of TRT with and without an aromatase inhibitor were conducted in men with **hyposexuality and seizure disorders**. One trial showed a significant benefit in sexual interest from the addition of testolactone therapy [*].
- A second trial involving 40 men reported a trend toward improved libido in men treated with T and anastrozole over T alone, although this did not reach statistical significance. Some men in the T-only group reported improvement in libido despite increases in E2 with TRT [**].

[*] Herzog AG, Klien P, Jacobs AR. Testosterone versus testosterone in treating reproductive and sexual dysfunction in men with epilepsy and hypogonadism. Neurology 1998;50: 782–4.
[**] Herzog AG, Farina EL, Drislane FW, Schomer DL, Smithson SH, Fowler KM, Dworetzky BA, Bromfeld EB. A comparison of anastrozole and testosterone versus placebo and testosterone for treatment of sexual dysfunction in men withepilepsy and hypogonadism. Epilepsy Behav 2010;17:264–71

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Elevated E2 During TRT: To Treat or Not To Treat? (4)

- The results of these studies should be interpreted with caution as it is not clear how this group compares with the larger group of T-deficient men. These men were all treated with antiepileptic drugs such as phenytoin and carbemazapime, which increase SHBG, likely through induction of hepatic synthesis, and may therefore impact androgen and estrogen concentrations and metabolism. Impotence, decreased libido, and infertility are common and associated with a deficiency in free T despite normal total T levels [*]. E2 levels are increased in hyposexual men with epilepsy compared with men with normal sexual function and with healthy controls [**].

[*] Toone BK, Wheeler M, Nanjee M, Fenwick P, Grant R. Sex hormones, sexual activity and plasma anticonvulsant levels in male epileptics. J Neurol Neurosurg Psychiatry 1993;46: 824–6
[**] Murialdo G, Galimberti CA, Fonzi S, Manni R, Costelli P, Parodi C, Solinas GP, Amoretti G, Tartara A. Sex hormones and pituitary function in male epileptic patients with altered or normal sexuality. Epilepsia 1995;36:360–5

Elevated E2 During TRT: To Treat or Not To Treat? (5)

- We therefore find no evidence to support the contention that relative reductions in E2 via the use of aromatase inhibitors or other agents in conjunction with TRT offer benefits beyond that offered by TRT alone.
- Anecdotally, in our practice, there have been rare cases of men who failed to experience symptomatic benefits from TRT and were found to have elevated E2 concentrations. Some of these men have responded to steps to lower E2 concentrations, either by reduction in T dosage or by addition of aromatase. However, these cases are anecdotal, and even if treatment was beneficial, the rarity of such occurrences does not justify the routine use of aromatase inhibitors together with TRT.
- Moreover, aromatase inhibitors may reduce E2 levels below a crucial threshold for bone health, and dual-energy X-ray absorptiometry (DXA) monitoring should therefore be considered for individuals receiving such therapy.

Conclusions

- E2 is essential to normal male sexual function in animals, however the data are inconclusive as to its effect in humans.
- There is some evidence that estrogens may contribute to the persistence of sexually stimulated erectile function when serum T is severely depressed, such as in men who have undergone castration for advanced prostate cancer men.
- It does not appear that naturally occurring elevations in E2 are harmful with respect to T levels or sexual function.
- E2 may increase during TRT, but elevations above the normal range are uncommon. Elevations in E2 may resolve with prolonged TRT.
- Symptoms of estrogen excess, such as gynecomastia or nipple tenderness, are rare.

Conclusions (2)

- Men who experience such symptoms should consider temporary or permanent discontinuation of TRT, or the addition of an aromatase inhibitor.
- We do not recommend the routine use of aromatase inhibitors with TRT.
- In the absence of signs of estrogen excess, we also find no reason to recommend the use of aromatase inhibitors in men who experience positive benefits from TRT despite elevated or high-normal E2 concentrations.
- When an aromatase inhibitor is used, it should be titrated so that E2 levels remain above 40 pmol/L to preserve bone health, and monitoring of bone mineral density with DXA is recommended.

Appendix 5

Estrogens and Fat in Men

Reference: F. Mauvais-Jarvis (ed.), Sex and Gender Factors Affecting Metabolic Homeostasis, Diabetes and Obesity, Advances in Experimental Medicine and Biology 1043.

Abstract

- Recent data from clinical intervention studies indicate that estradiol may be a stronger determinant of adiposity than testosterone in men, and even short-term estradiol deprivation contributes to fat mass accrual

Introduction

- Aromatase is expressed broadly throughout central and peripheral tissues including brain and adipose tissue and skeletal muscle; therefore, through local aromatase activity in key metabolic tissues, estrogen production is regulated in tissue-specific fashion

Clinical Intervention Studies

- One small study examined the effects of testosterone replacement in obese men with low-normal baseline serum testosterone concentrations.
- Whereas treatment with testosterone gel led to significant reductions in adiposity, these changes were not seen when testosterone was co-administered with an aromatase inhibitor (Juang et al. 2014).
- In a larger study of healthy men, two subject cohorts were administered the GnRH analogue goserelin acetate to suppress endog-enous sex steroid production.

Clinical Intervention Studies

- Simultaneously, subjects in the first cohort received either placebo gel or variable doses of add-back testosterone gel, and the second cohort of subjects received either placebo gel or testosterone gel with an aromatase inhibitor.
- Strikingly, whereas androgen exposure appeared to mediate changes in lean mass, estradiol rather than testosterone was found to be the primary determinant of changes in fat mass (Finkelstein et al. 2013).
- Subsequently, another clinical study similarly enrolled healthy, eugonadal men and rendered them medically castrate through use of the GnRH antagonist acyline.

Clinical Intervention Studies

- Subjects in this study variably received placebo gel, low-dose or full replacement dose testosterone gel, or full replacement dose testosterone gel with an aromatase inhibitor.
- In all three treatment groups rendered sex steroid deficient, significant increases in body fat mass were evident within only 4 weeks of drug treatment (Chao eta!. 2016).
- Again, estradiol rather than testosterone deprivation exhibited a stronger correlation with the observed increases in adiposity.

Implications for Clinical Practice

- Another population for whom the metabolic effects of estradiol could prove highly relevant are men with prostate cancer.
- In the USA, prostate cancer affects 2 million men, and up to 50% of these men will undergo androgen deprivation therapy (ADT) at some point in their treatment course (Meng et al. 2002).
- The most common form of ADT involves GnRH analogues that confercentral hypogonadism, and over the past decade, clinical evidence has compellingly demonstrated the men undergoing ADT are at substantially higher risk of increased adiposity, insulin resistance, T2DM, and cardiovascular disease than age-matched controls with or without prostate cancer (Cannata et al. 2012; Hamilton et al. 2011; Keating et al. 2006, 2012; Shahani et al. 2008).

Implications for Clinical Practice

- ADT-induced hypogonadism is a state of both androgen and estrogen deficiency, and the latter is now believed to contribute substantially to the metabolic dysregulation evident in men receiving GnRH analogues.
- Interestingly, estradiol therapy was among the ADT formulations originally used for treatment of prostate cancer (Cannata et al. 2012), and interest in estrogen-based ADT recently has been renewed as it could effectively suppress androgen production while reducing the metabolic sequelae of GnRH analogues (Phillips et al. 2014)

Appendix 6

Calculated Free T and T:E Ratio but not Total Testosterone and Estradiol Predict Low Libido

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Reference: Presented By Nikhil Gupta, Springfield, IL
at the 2017 AUA Annual Meeting - May 12 - 16, 2017 – Boston, Massachusetts, USA

Introduction

- Libido is thought to be influenced by hormonal milieu, particularly testosterone.
- The knowledge about the role of estradiol in male sexual function has been found to be more important than originally thought.
- **The estradiol cut-off point of 50 pg/ml in hypogonadal men is thought to directly affect libido.**
- Dr. Gupta presented a study assessing the impact of sex hormones on libido specifically in a cardiac patient population.

Patient Population and Tools

- The study focused on 200 men in a cardiology practice who completed the IIEF-15, ADAM, and previous ED treatment questionnaires.
- Additionally all patients had serum total testosterone (T), estradiol (E), and sex hormone binding globulin (SHBG) levels measured via morning lab draws.
- Their free testosterone (CFT) was calculated using an online ISSM calculator.
- Patients that were diagnosed for hypogonadism in the past or who were currently on medications possibly affecting T levels were excluded.
- Hormonal levels were correlated to responses to the IIEF questions 11 and 12 (IIEF11, IIEF12), focusing on libido.

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Results

- Results demonstrated the mean total T level to be 310 ng/dL with CFT of 5.4 ng/dL. Mean E levels were 4.4 ng/dL and mean T:E ratio was 8.2.
- Importantly, 55% of patients had T levels less than 300 ng/dL and 74% of patients had a CFT < 6.5 ng/dL.
- Negative correlation was found between estradiol and IIEF11 and IIEF12, but was not statistically significant.
- However, **a positive correlation was found between IIEF11 and IIEF12 and CFT and T:E ratio (p=0.007, p=0.009, respectively).**
- At a cutoff of E=50 pg/mL, no difference was found for either hypogonadal or eugonadal men on the IIEF11 or IIEF12.

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Calculated Free T and T:E Ratio but not Total Testosterone and Estradiol Predict Low Libido

- In summary, **free T and T:E ratio were predictive of positive libido response** on IIEF11 & 12 questions in the IIEF questionnaire.
- Estradiol, even at a cutoff of 50 pg/ml, was not independently associated with improved libido.
- Surprisingly, **no correlation was found between total testosterone and IIEF11 (desire frequency).**
- The effect of testosterone and estradiol on libido requires further research with prospective studies.

Reference: Presented By Nikhil Gupta, Springfield, IL
at the 2017 AUA Annual Meeting - May 12 - 16, 2017 – Boston, Massachusetts, USA

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Clinic Optimizers Services

INTEGRATIVE CLINICAL SUPPORT

CO offers product information, clinician education and treatment application protocols for commonly compounded prescribed medications. CO is trusted by FDA registered 503b and by PCAB certified 503a compounding pharmacies to provide physicians an educational resource and personalized support to help supplement their practices and to customize their patients' treatment options. Educational topics include:

- Testosterone Replacement Therapy (TRT) in men and women
- HPTA management in men
- Hormone Replacement therapy using compounded products
- Estrogen management using aromatase inhibitors and SERMS
- Compounded adrenal and thyroid products
- Growth Hormone secretagogue use and dosing
- Weight-Management programs
- IV and Injectable nutrition implementation and practice
- Hormone and wellness blood testing and monitoring schedules
- Platelet Rich Plasma Injections and marketing
- Stem Cell treatments
- Hair Restoration

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Clinic Optimizers Services (Cont.)

LABORATORY ACCESS & SUPPORT

Clinic Optimizers can assist with hormone testing including what methodology to use, what tests to order, and how to use them to administer, titrate, and monitor hormone and related therapies. In addition, CO provides clinics with access to low cost lab testing through a nationally recognized laboratory.

VENDOR REFERRAL & MANAGEMENT

Clinic Optimizers has established relationships with key vendors that are vital to practices that focus on HRT and wellness therapies. Contact us if you would like to be referred to one or more of the following resources:

- FDA registered 503b compounding pharmacy for office use medications
- PCAB accredited 503a compounding pharmacy for patient-specific medications
- Wholesale lab tests through nationally located laboratories
- Access to medical supply wholesalers

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