

Male Hypogonadism

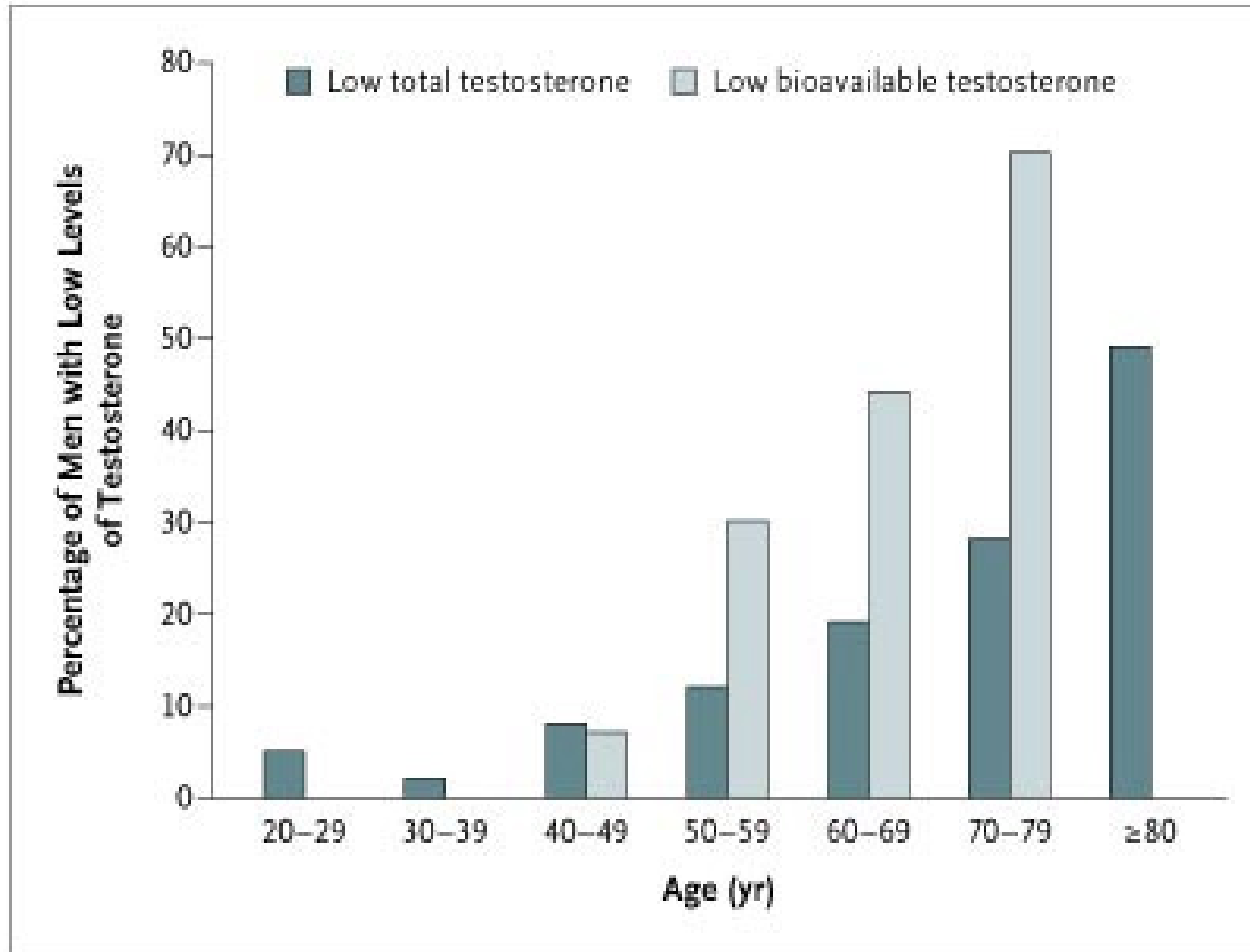
**FINANCIAL DISCLOSURES:
NONE**

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April 29, 2008**



Prevalence of Testosterone Deficiency



Male Hypogonadism: Clinical Features

Low serum testosterone

<300 ng/ml in men <50; <200 ng/ml in older men

- **Sexual symptoms**
 - **Decreased libido**
 - **Erectile dysfunction**
- **Decreased muscle mass and strength**
- **Bone loss**
- **Decreased energy or stamina, sense of “vitality”**
- **Fatigue, depression, impaired cognition**



Anemia

Testosterone Deficiency in Men

PREPUBERTAL

- Hypothalamic or pituitary disorders (Kallmann's syndrome, craniopharyngioma)
- Testicular disorders (Klinefelter's syndrome)
- Enzymatic deficiency (aromatase deficiency)

POST-PUBERTAL

- **Aging**
- Systemic diseases
- Drugs (GnRH agonists, chemotherapy, glucocorticoids)
- Hypopituitarism
- Testicular failure



Benefits of Testosterone Therapy

- Improved libido
- Improved muscle mass and decreased fat mass
- Increased strength ??
- Improved sense of well being
 - No improvement of cognition or depression
- Increased bone density

NOTE: These effects have only been documented in men with low testosterone



Effects of Testosterone Therapy

43 healthy young men, average age 27

Testosterone enanthate 600 mg weekly or placebo for 10 weeks

<u>VARIABLE</u>	<u>NO EXERCISE</u>		<u>EXERCISE</u>	
	<u>PLACEBO</u>	<u>TESTOSTERONE</u>	<u>PLACEBO</u>	<u>TESTOSTERONE</u>
Serum T ng/dl				
Baseline	516	502	557	431
10 weeks	453	2828	667	3244
Hemoglobin g/dl				
Baseline	14.9	15.1	14.5	15.3
10 weeks	15.0	15.5	14.3	15.7



Effects of Testosterone Therapy – 10 Weeks

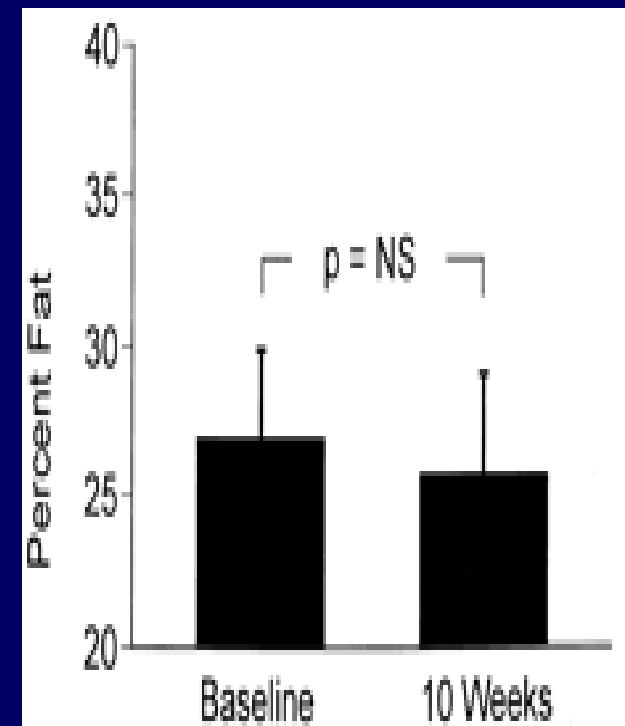
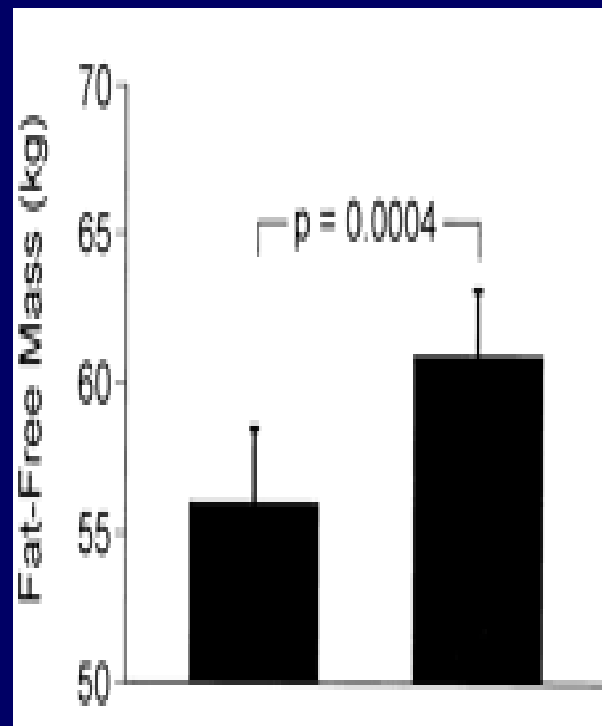
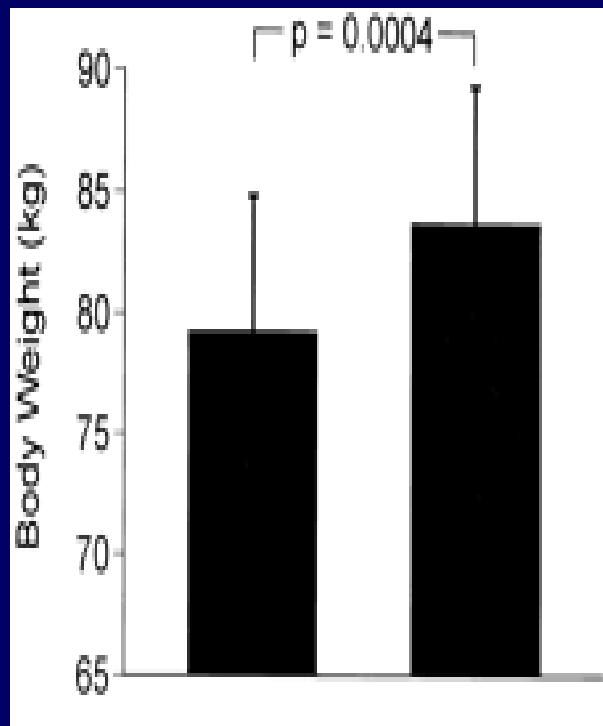
<u>VARIABLE</u>	<u>NO EXERCISE</u>		<u>EXERCISE</u>	
	<u>PLACEBO</u>	<u>TESTOSTERONE</u>	<u>PLACEBO</u>	<u>TESTOSTERONE</u>
LDL cholesterol mg/dl				
Baseline	113	133	117	128
10 weeks	116	133	115	121
HDL cholesterol mg/dl				
Baseline	39	37	42	40
10 weeks	36	34	37	36
Triglycerides mg/dl				
Baseline	155	147	105	146
10 weeks	139	111	104	125



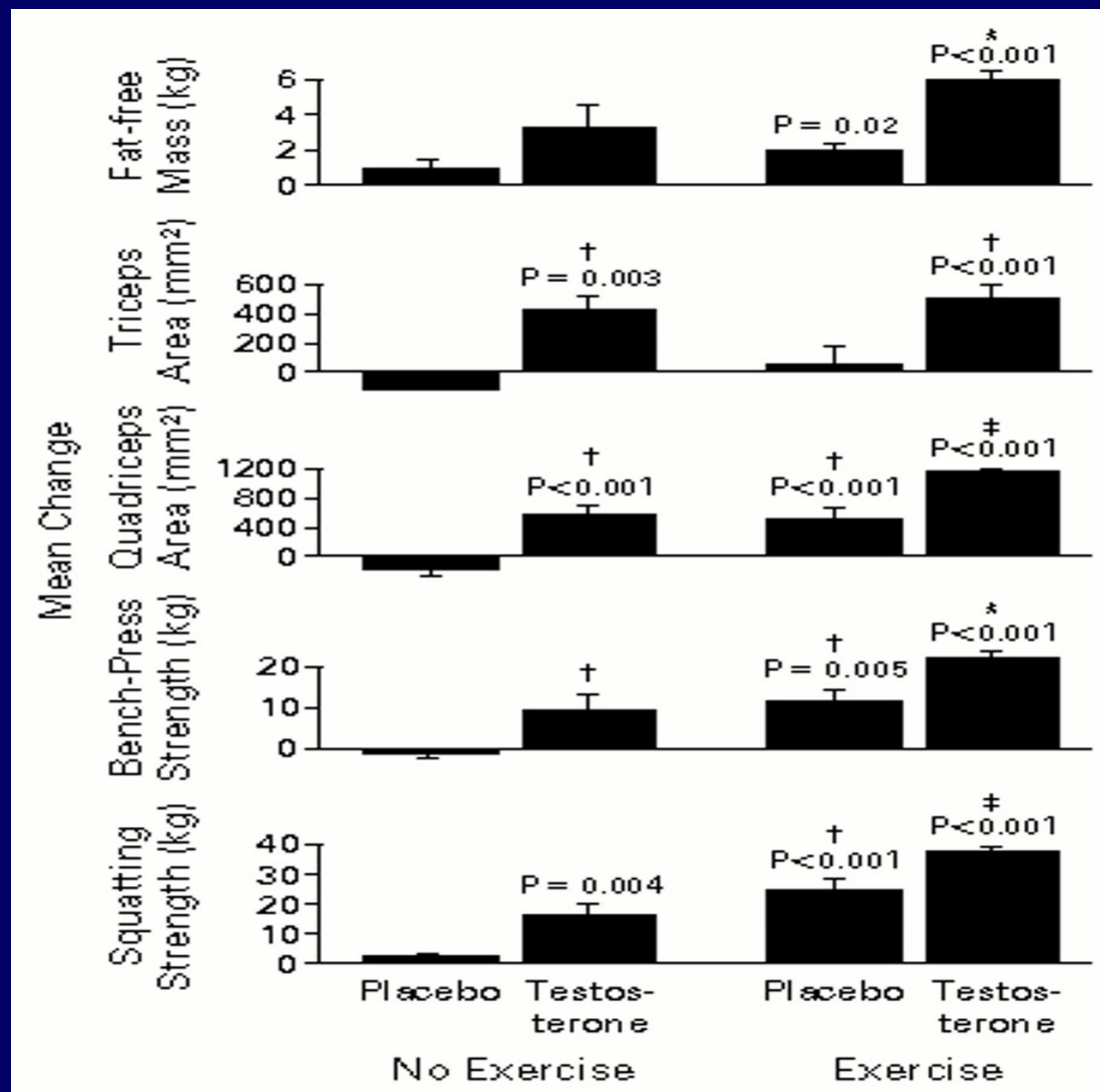
Effects of Testosterone Therapy – 10 Weeks

7 hypogonadal men

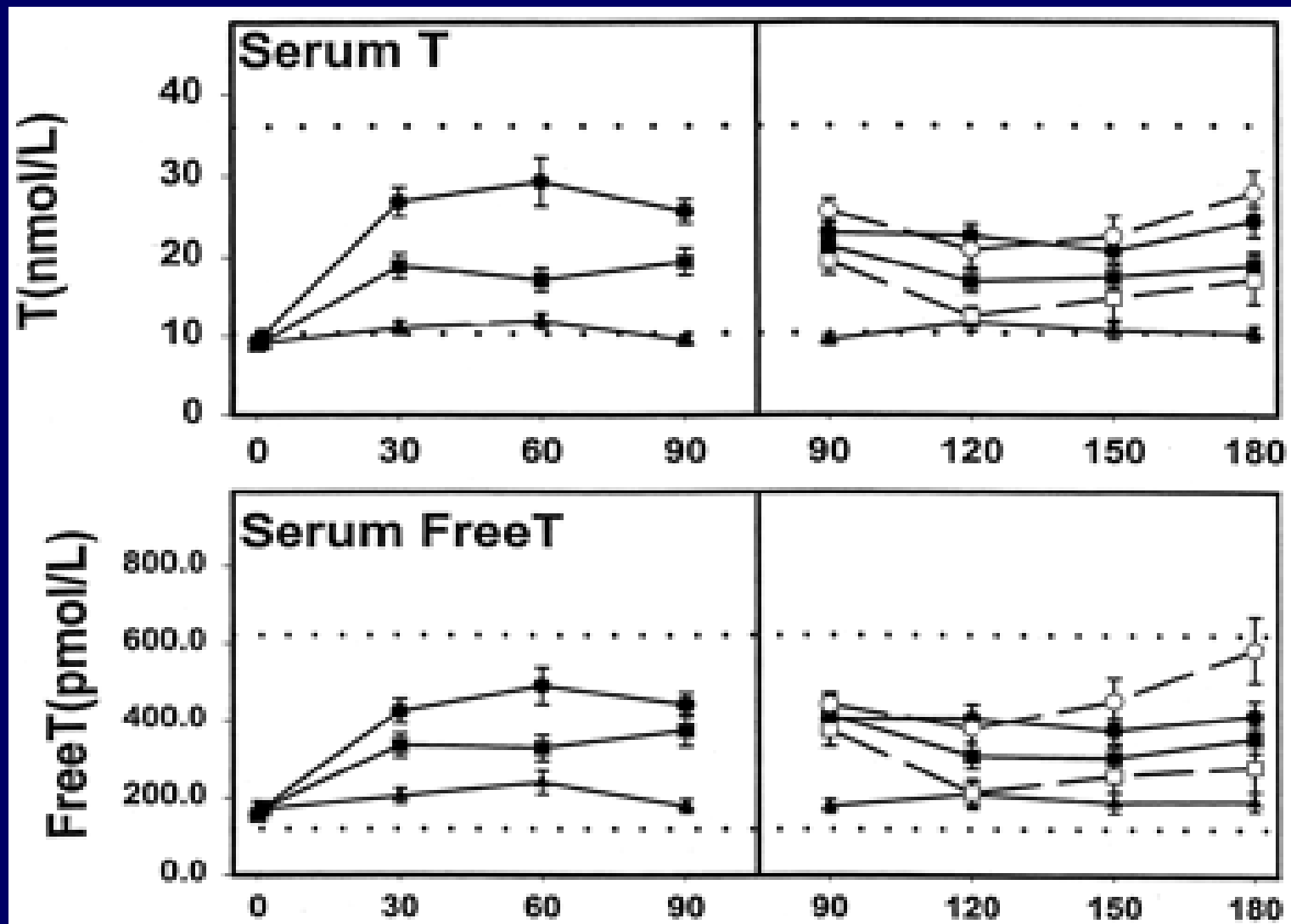
Testosterone enanthate 100 mg/week x 10 weeks



Effects of Testosterone Therapy – 10 Weeks

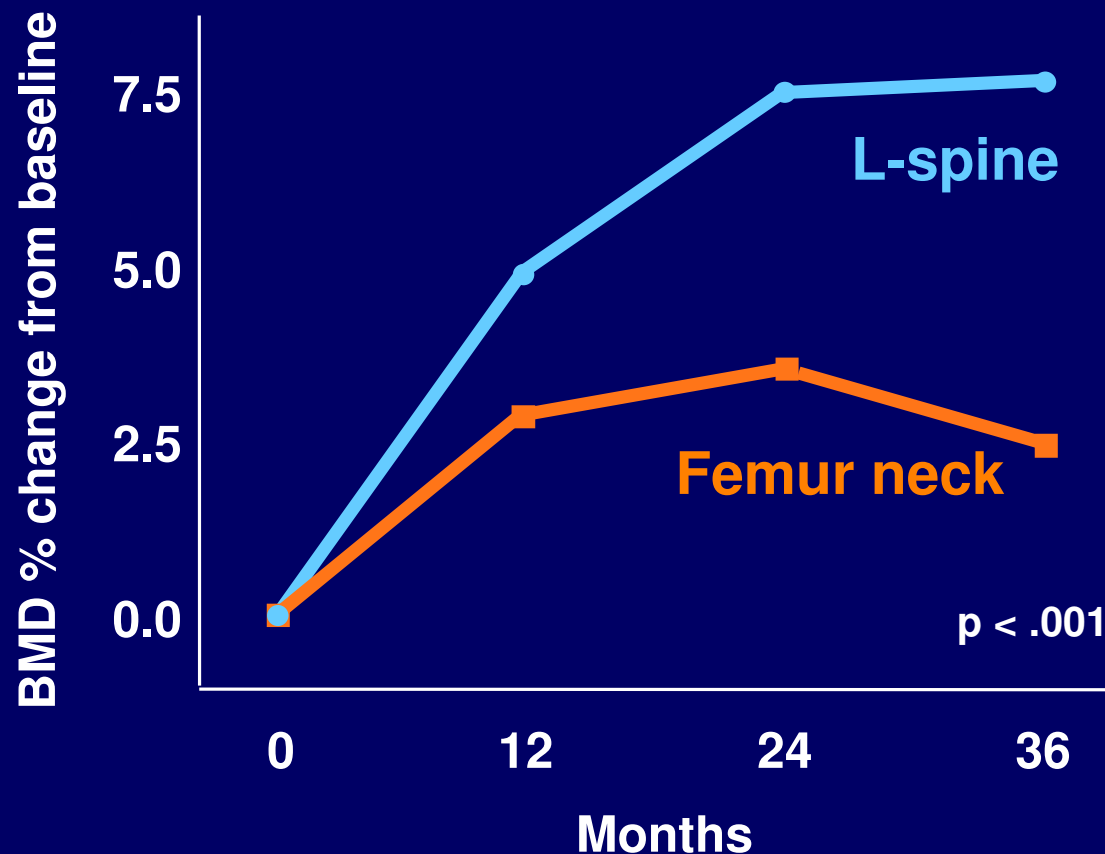


Transdermal Testosterone Therapy



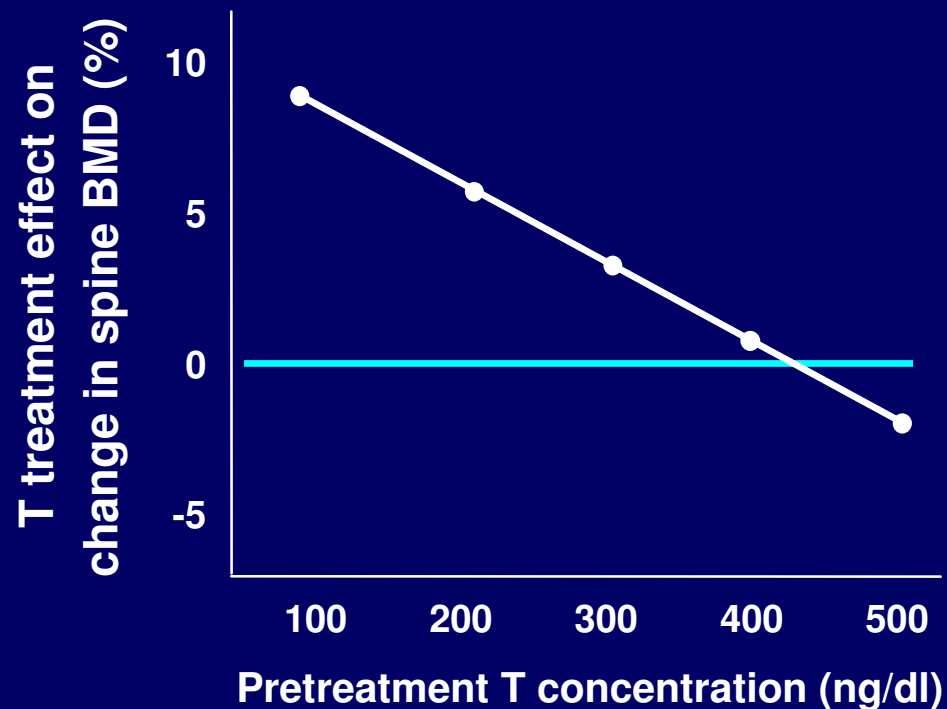
Testosterone Therapy: Bone Density

- 108 men over 65, serum testosterone less than 475 ng/dl and LS T-score less than 0
- 3 year double-blind, placebo controlled trial of T patch



Testosterone Therapy: Bone Density

3 year double-blind, placebo controlled trial of T patch



Alendronate Treatment of Osteoporosis in Men

- **241 men with low BMD randomly assigned to receive placebo or alendronate 10 mg daily for 2 years**
- **30% of men had low BMD levels**
- **Baseline markers of bone metabolism were not different between those with or without testosterone deficiency**
- **Changes in bone density, biochemical markers of bone turnover and fracture reduction were the same in men with normal vs low serum testosterone levels**



Risks of Testosterone Therapy

- **Simulation of prostate growth** Rarely of significance
- **Hyperlipidemia** Not seen with physiological doses
- **Cardiovascular risks** No evidence of harm; possible benefit
- **Venous thrombosis** No clinical evidence
- **Polycythemia** Mainly in men with COPD
- **Worsened sleep apnea** Infrequent
- **Testicular atrophy** Irrelevant, reversible
- **Acne & increased body hair** Mild, dose-related
- **“Testotoxicosis”** Only with excess doses
- **Hepatotoxicity** Only with oral therapy



Initiating Testosterone Therapy

- **Careful assessment and recording of symptoms**
 - **Libido**
 - **Strength, stamina and energy**
 - **Well being**
- **Rectal exam and/or PSA**
- **Hematocrit**

- **Lipid panel - optional**
- **Bone density - optional**



Monitoring Testosterone Therapy

Follow-up at 1- 2 months

- **Symptom assessment**
 - **Libido**
 - **Strength, stamina and energy**
 - **Well being**
- **PSA**
- **Hematocrit**
- **Serum testosterone**



Testosterone Replacement Therapy

- Prevalence of testosterone deficiency increases with age
- Clinical effects of this physiological abnormality is difficult to judge.
- Symptoms and signs have only been associated with frank hypogonadism (T values generally <200 ng/dl)
- Meaningful benefits have not been documented
- Many hypogonadal men do not improve with therapy
- Risks have not been adequately assessed
- Osteoporosis is not an indication for testosterone therapy



Testosterone Replacement Therapy

CONCLUSIONS

- **There is no justification for use of testosterone therapy in men who do not have low serum testosterone levels.**
- **Treatment should be considered only when low testosterone levels are associated with compatible symptoms.**
- **If no symptomatic response occurs after 2-3 months, discontinue therapy.**



References

1. Rhoden EL, Morgentaler A. Risks of testosterone-replacement therapy and recommendations for monitoring. *N Engl J Med* 2004;350:482-492.
2. Vermeulen A. Androgen replacement therapy in the aging male – a critical evaluation. *J Clin Endocrinol Metab* 2001;86:2380-2390.
3. Nankin HR. Hormone kinetics after intramuscular testosterone cypionate. *Fertil Steril* 1987;47:1004-1009.
4. Sokol RZ, Palacios A, Campfield LA, Saule C, et al. Comparison of kinetics of injectable testosterone in eugonadal and hypogonadal men. *Fertil Steril* 1982;37:425-430.



Outline

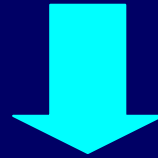
Table 2. Potential Risks Associated with Testosterone-Replacement Therapy.

Potential Risk	Comments
Cardiovascular disease	Existing evidence suggests a neutral or possible beneficial effect
Lipid alterations	Most studies show no change with physiologic replacement doses
Erythrocytosis	Wide range of risk, depending on mode of administration: 3–18% with transdermal administration, up to 44% with injection; requires monitoring
Fluid retention	Rarely of clinical significance
Benign prostatic hyperplasia	Rarely of clinical significance
Prostate cancer	Controversial; unknown level of risk; requires long-term monitoring
Hepatotoxicity	Limited to oral agents, which are infrequently used in the United States
Sleep apnea	Infrequent
Gynecomastia	Rare, usually reversible
Skin reactions	High incidence with patch (up to 66%), low incidence with gel (5%), rare with injections
Acne or oily skin	Infrequent
Testicular atrophy or infertility	Common, especially in young men; usually reversible with cessation of treatment

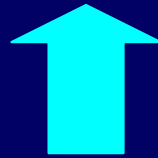


Paths to Bone Loss in Prostate Cancer

Surgical/radiologic
orchectomy



Gonadal Steroid Deficiency



GnRH agonists

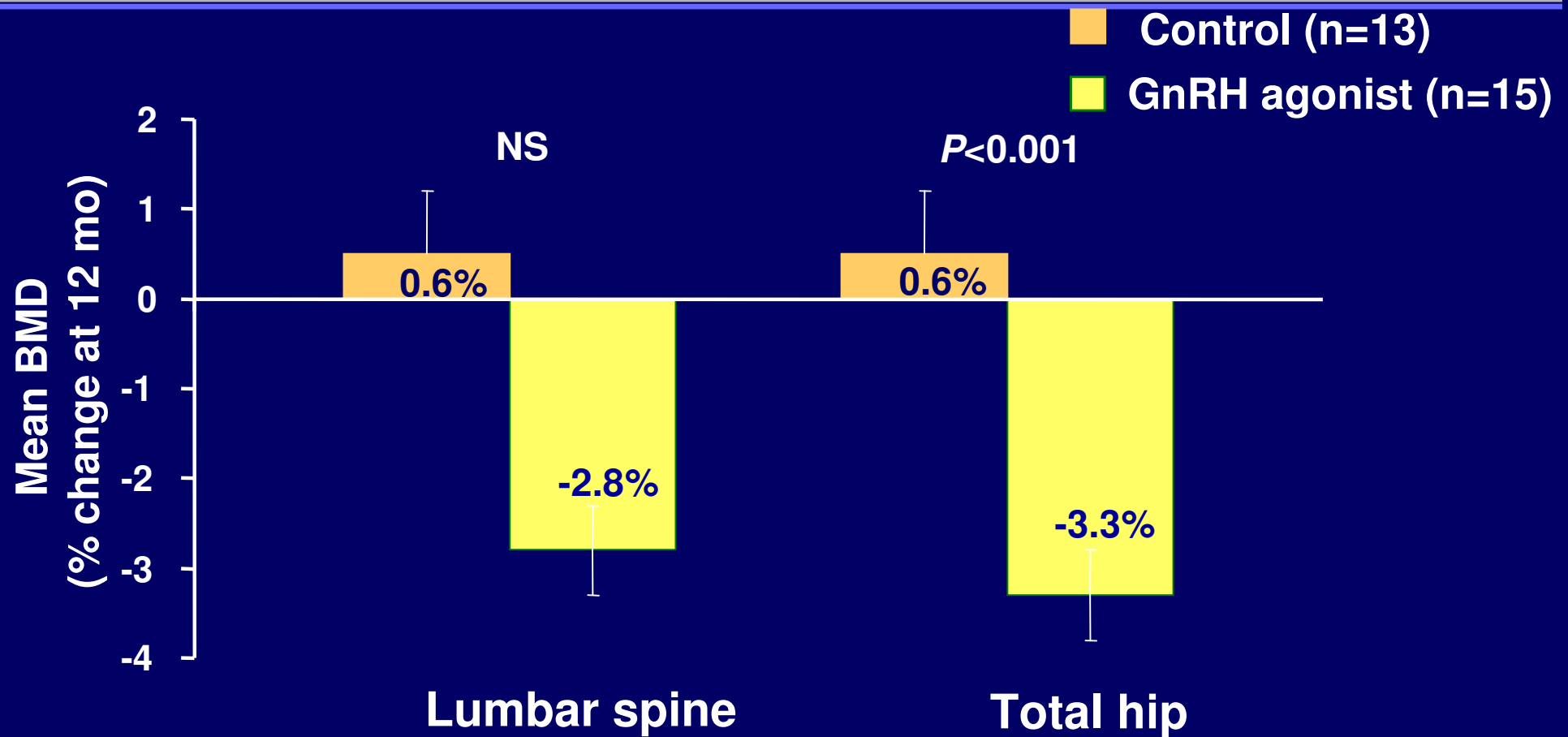
Leuprolide
Goserelin
Nafarelin



Anti-androgens



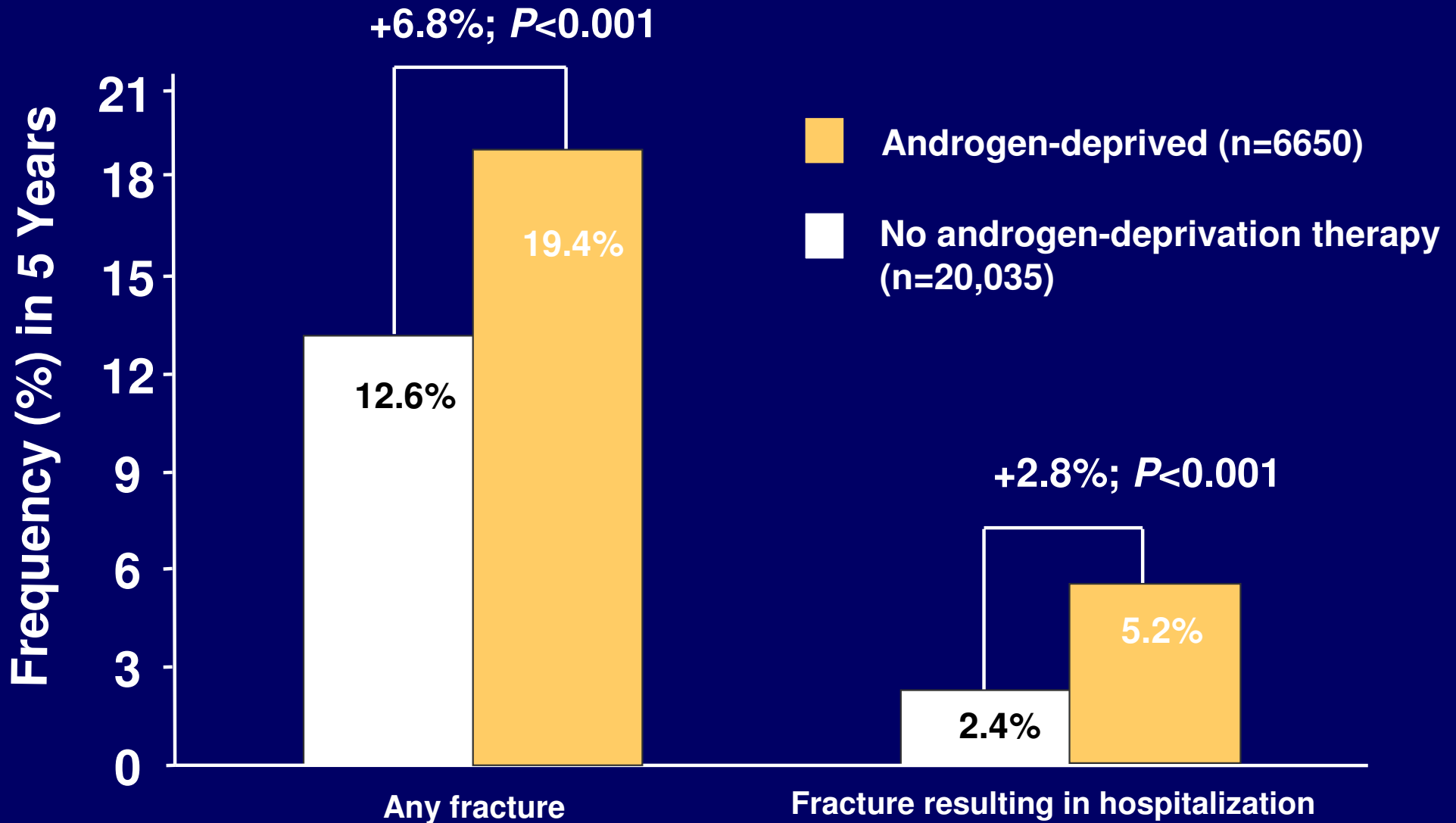
GnRH Agonist Therapy Decreases BMD in Men with Prostate Cancer



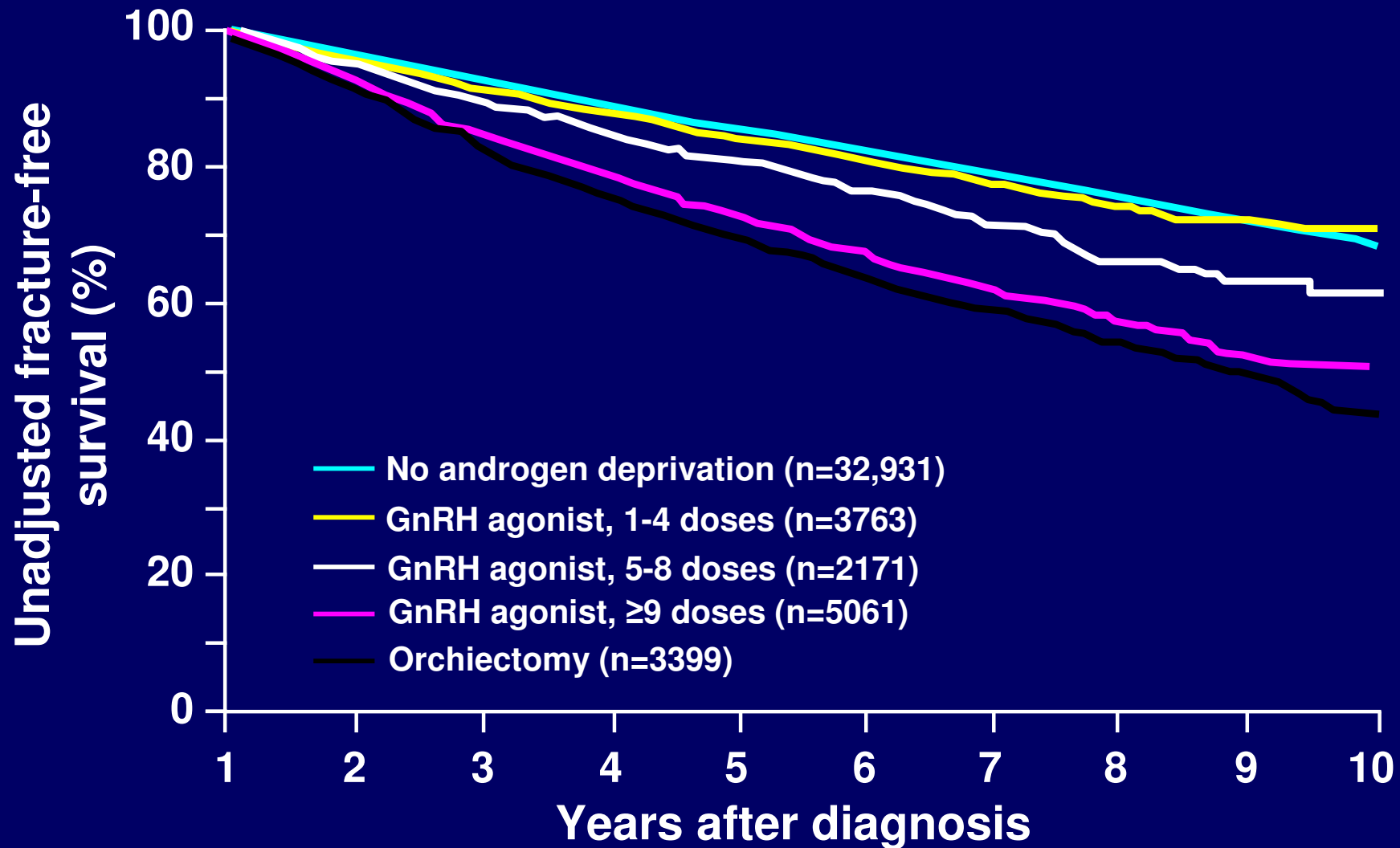
NS = not significant



Fractures with Prostate Cancer Diagnosis



Fracture-Free Survival Diminishes With Time and Cumulative Use of GnRH



Prevention of Bone Loss in Men with Prostate Cancer Treated with Androgen Deprivation Therapy*

* Off label drug use

Oral Bisphosphonates in Men on Androgen Deprivation Therapy

- Alendronate and risedronate effective in men with low BMD with or without hypogonadism
- No randomized, controlled trials in men with prostate cancer
 - chart review study of 47 men on androgen deprivation therapy: no bone loss in hip and spine if on alendronate 70mg/week vs. decrease in BMD if on no antiresorptive medication*



Prevention of Bone Loss Due to Androgen Deprivation Therapy with Alendronate

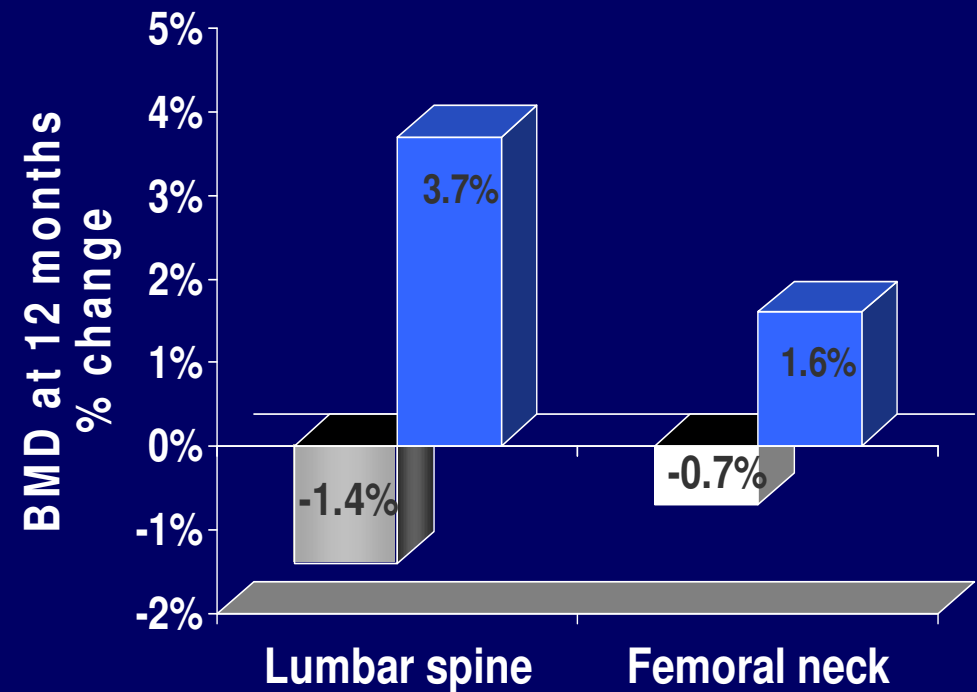
N= 112 men

Mean age: 72

Alendronate 70 mg Q week or placebo

Calcium + vitamin D

Interval: 1 year



Bone Loss in Cancer Patients Treated with Androgen or Estrogen Deprivation

- Sex steroid-deprivation therapy leads to rapid bone loss and increases fracture risk
-
- Bisphosphonates appear to be effective in preventing bone loss - impact on fracture risk not known
 - not FDA approved for this indication
- Skeletal consequences should be considered in all patients beginning hormone deprivation therapy.
- ? if bone density testing helpful in making treatment decisions

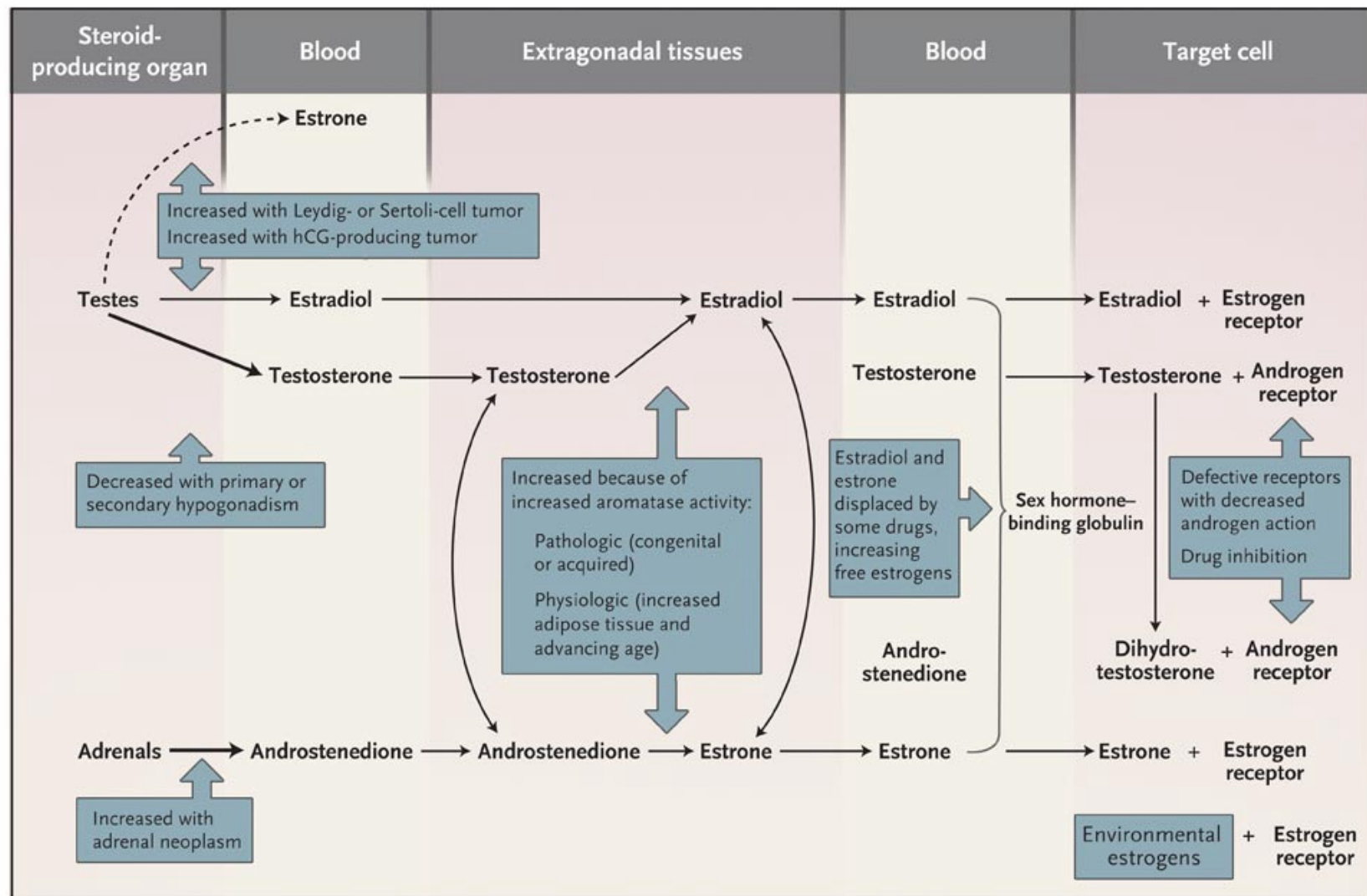


Gynecomastia: Case Vignette

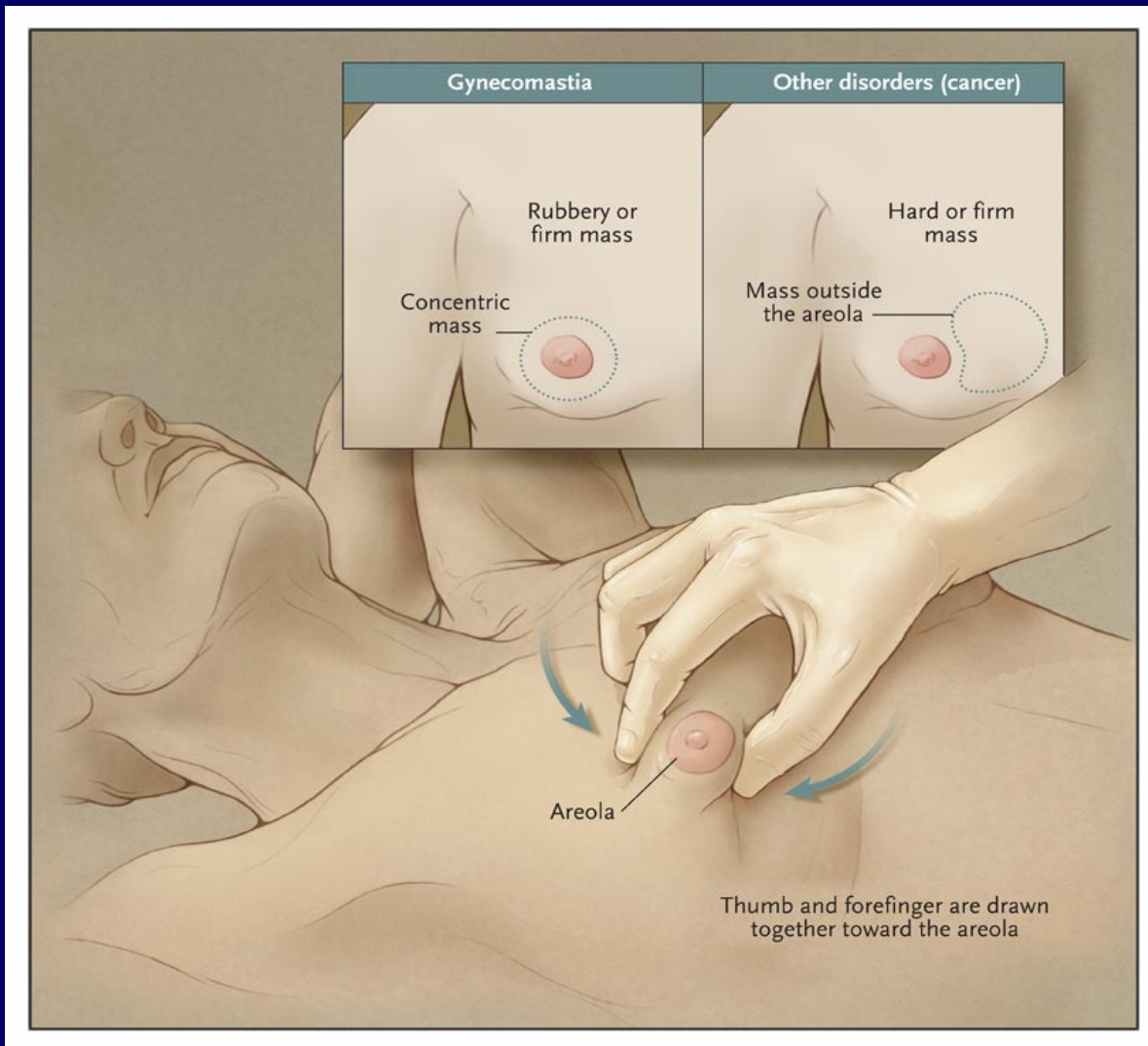
- During an evaluation for low back pain, a 67-year-old man is found to have gynecomastia on the right side that is nontender on palpation.
- Other than a body-mass index (the weight in kilograms divided by the square of the height in meters) of 32, the physical examination is normal.
- His medical history is notable only for hyperlipidemia; his only medication is a statin.
- How should his gynecomastia be evaluated and managed?



Estradiol and Estrone, Displaced by Some Drugs, Resulting in an Increase in Free Estrogen



Differentiation of Gynecomastia from Pseudogynecomastia and Other Disorders



Pseudogynecomastia

lipoma

epidermal inclusion cyst

pseudoangiomatous

stromal hyperplasia

intraductal papilloma

Evaluation:

mammography

ultrasound

biopsy

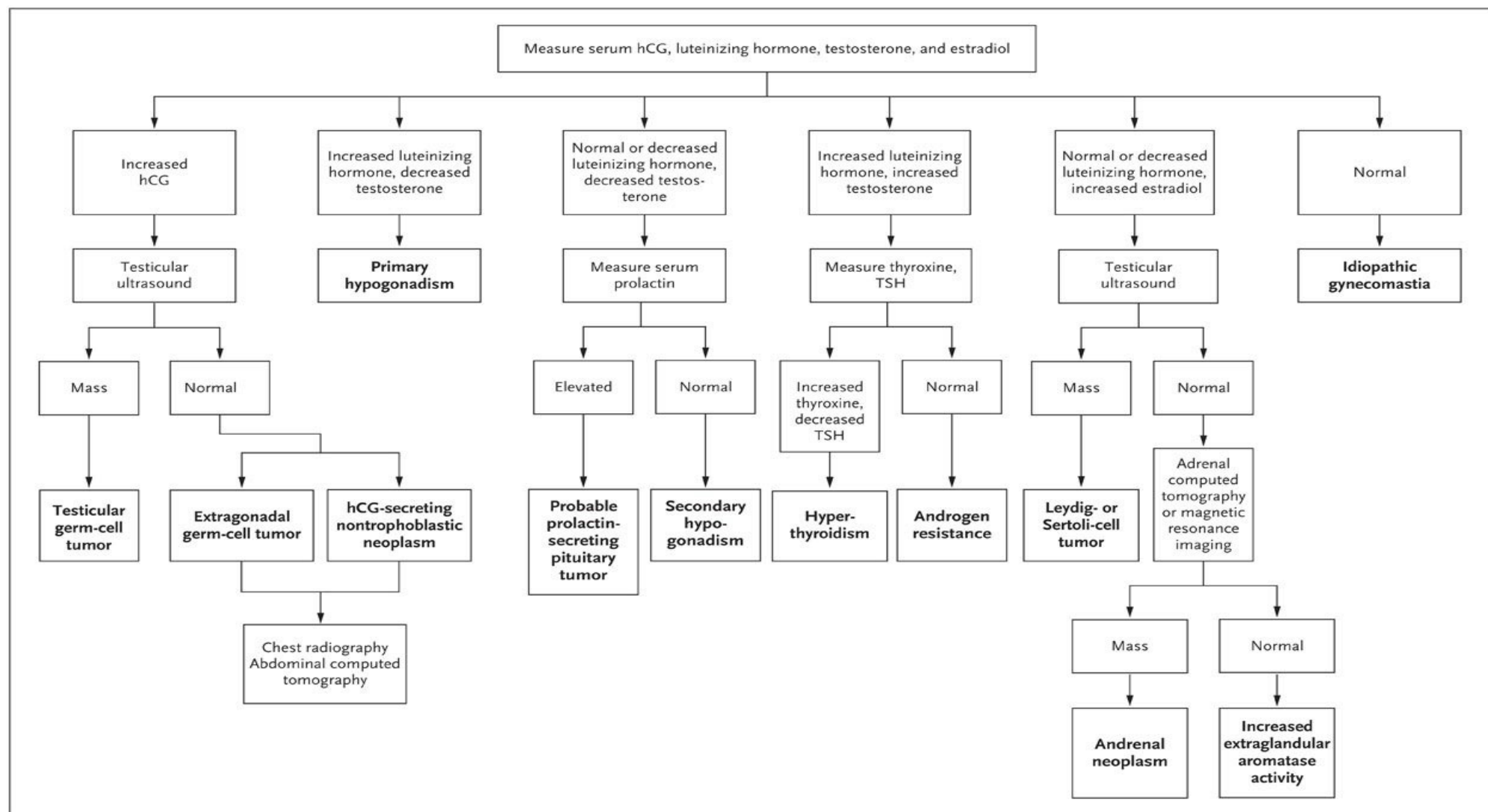


Braunstein G. N Engl J Med 2007;357:1229-1237



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Interpretation of Serum Hormone Levels and Recommendations for Further Evaluation of Patients with Gynecomastia



Gynecomastia: Evaluation

- **Gynecomastia vs mass**
- **Clinical history:**
 - **Duration**
 - **General health**
 - **Sex status**
 - **Drugs**
- **Lab:**
 - **Serum T, LH**
 - **Other tests if breast enlargement is unexpected**



Conclusions and Recommendations

- During the acute florid stage of gynecomastia, a trial of tamoxifen, at a dose of 20 mg per day for up to 3 months, may be attempted.
- If the gynecomastia has not regressed by 1 year, or in patients who present with long-standing gynecomastia who are troubled by their appearance, surgical removal of the breast glandular tissue and subareolar fat is an option that has a good cosmetic result in the majority of patients.
- For a patient such as the man in the vignette, who is asymptomatic, is not bothered by his gynecomastia, and does not have a suggestive history or physical examination, a more minimalist evaluation (i.e., measurements of testosterone and luteinizing hormone levels, although even the use of these tests might be debated) is recommended, and treatment other than weight reduction is not warranted for the gynecomastia.

