Testosterone: Applying New Research to Inform Clinical Practice

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Disclosures

- Biozen Board of Directors- Advisor for phase 2 clinical trials for a novel treatment of gynecomastia

Slides available if requested by 12/1/2025

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Case #1

A 20-year-old man reports declining libido over the past 18 months. He reports onset of puberty at age 13. He also reports decreased early morning erections and bilateral breast tenderness for 6 months. He has shaves twice weekly. His medical history is unremarkable.

Case #1

On physical examination, height is 72 in (183 cm) and BMI is 23 kg/m^2. He is clean shaven and has scanty axillary hair and pubic hair. There is tender, bilateral gynecomastia that is 3 cm in diameter, and there is no expressible galactorrhea.

He has a normal phallus with no hypospadias. His testes are 3 cc bilaterally.

https://www.endocrine.org/store/medical-instruments-and-models/orchidometer#

Classic Klinefelter Syndrome

Testis Size < 4 cc; normal is ≥ 15 cc

Matsumoto AM, Anawalt BD, Williams Textbook of Endocrinology, 14th Edition:668-755, 2020

Case #1

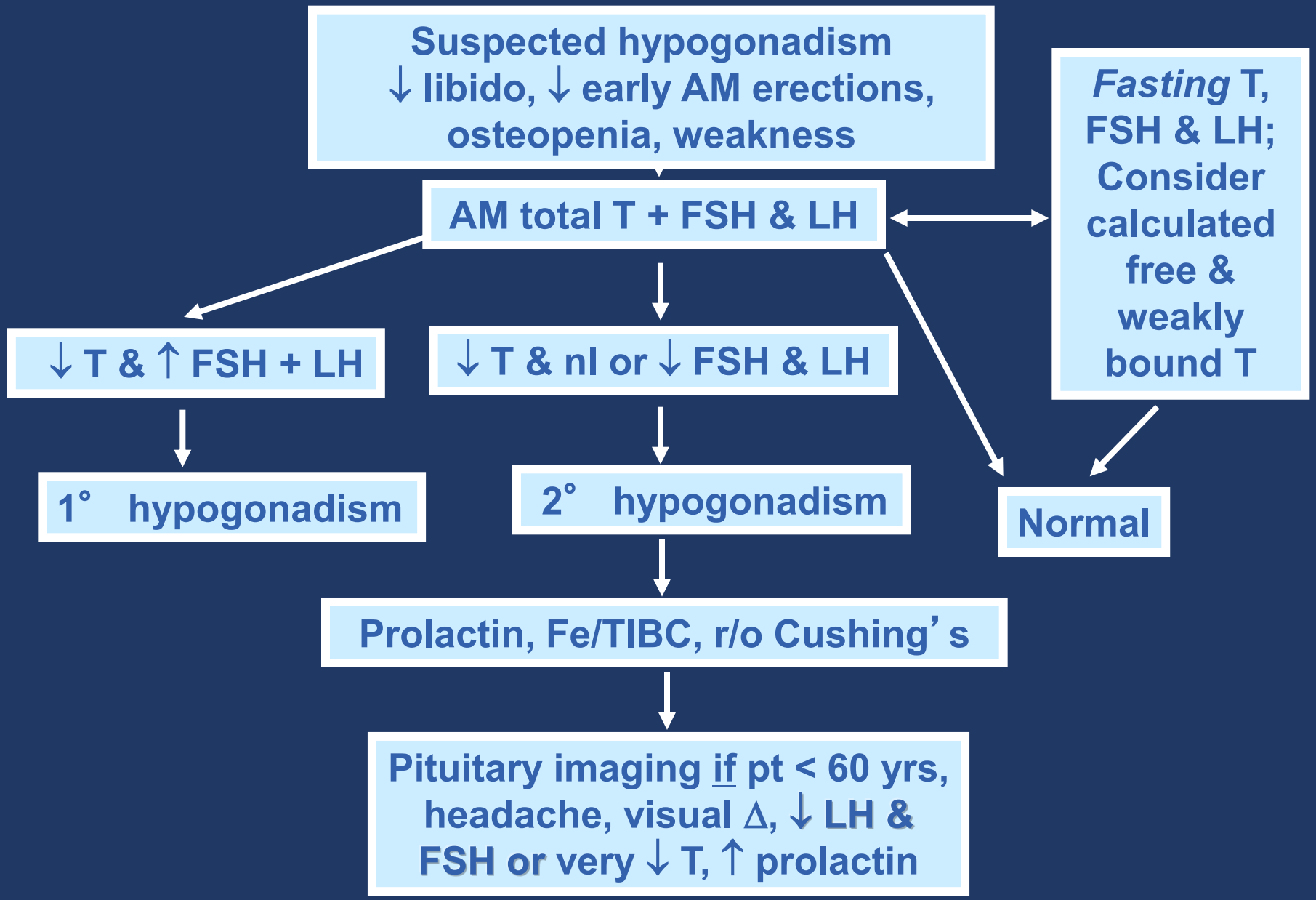
Labs:

Serum testosterone	175 ng/dL (264-916 ng/dL)
	6.1 nmol/L (9.2-31.8 nmol/L)
Serum FSH	35.0 mIU/mL (1.0-7.0 mIU/mL)
Serum LH	28.0 mIU/mL (1.0-9.0 mIU/mL)

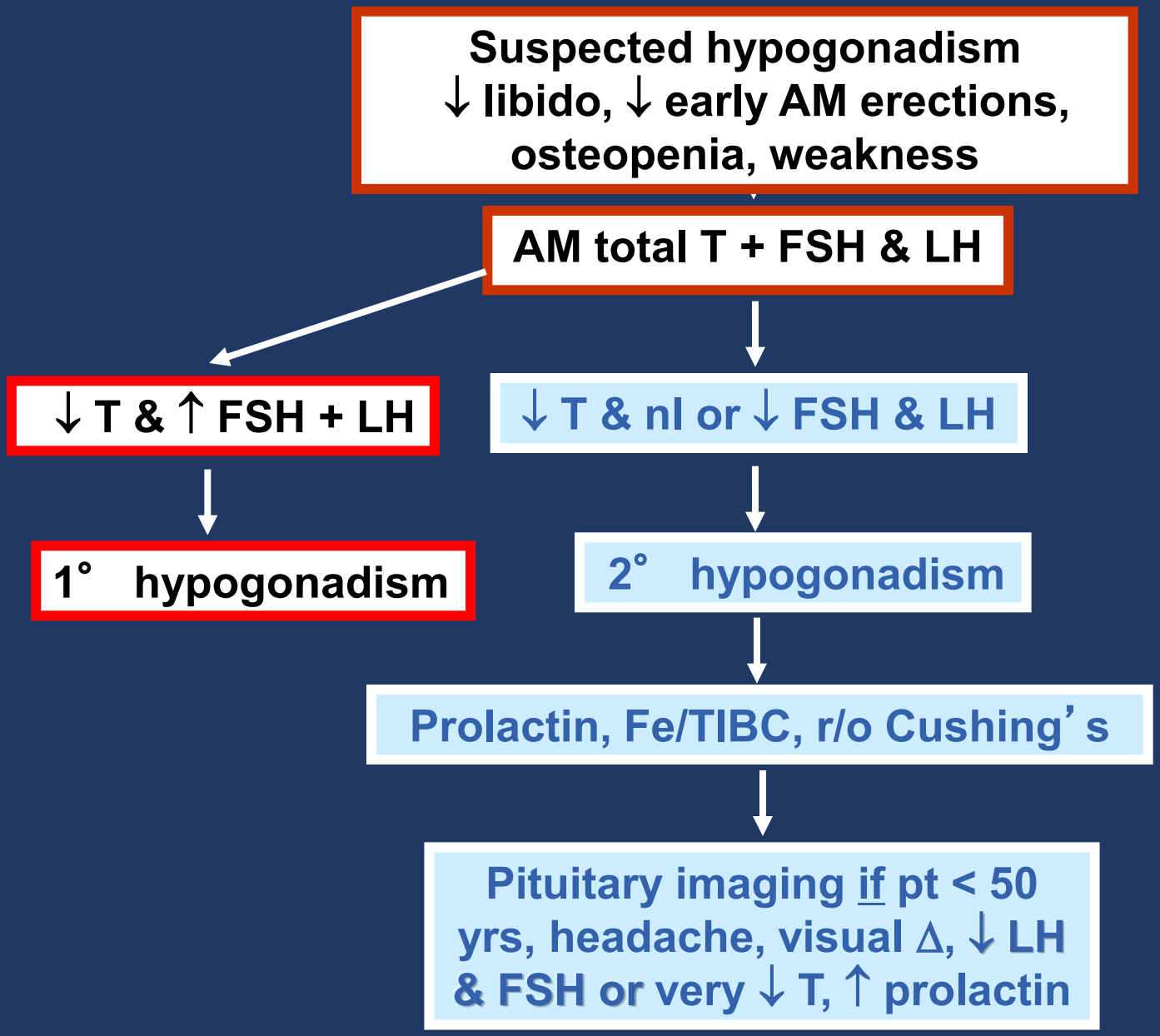
What is his likely diagnosis?

A. Klinefelter syndrome
B. Kallmann syndrome
C. Secondary hypogonadism due to FSH-secreting macroadenoma
D. Primary hypogonadism due to mumps orchitis or vaccine
E. Primary hypogonadism due to Covid

Hypogonadism algorithm



Hypogonadism algorithm



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Case #1

Based on the evidence from placebo-controlled trials, which of the following would be the most useful to help determine whether to initiate testosterone therapy?

a) Hemoglobin A1c
b) Bone densitometry by DXA
c) Bone densitometry with trabecular bone score (TBS)
d) Hematocrit
e) None of the above

Case #1

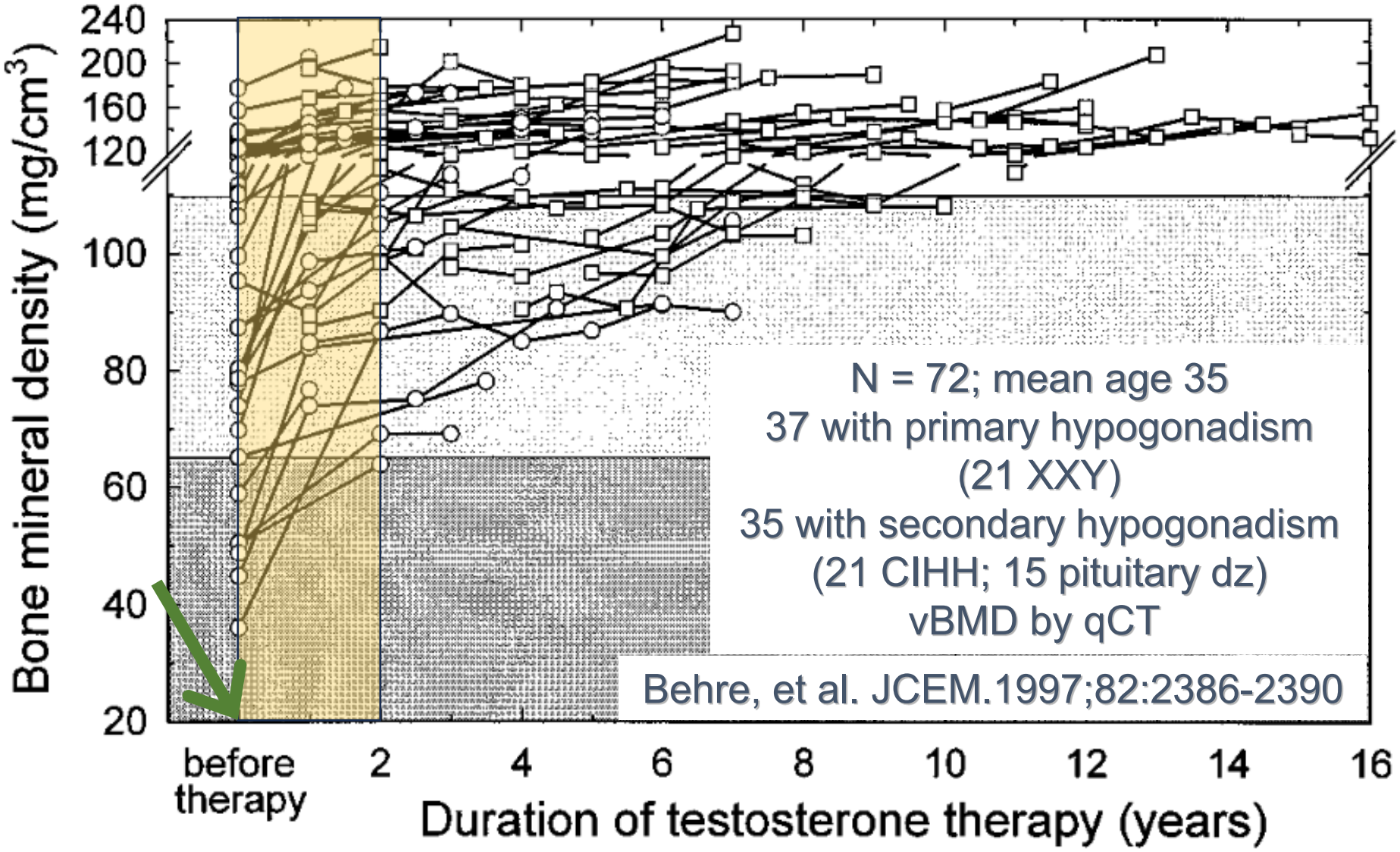
He begins testosterone therapy. A month later he returns to clinic because he saw on Reddit that testosterone might increase the risk of bone fractures. He is very active and has not had any fractures. What do you tell him?

TRAVERSE (the study that he is referring to) did not include men with Klinefelter syndrome (or other forms of hypothalamic-pituitary axis [HPT] disease) or severe hypogonadism. The men in TRAVERSE had low serum testosterone concentrations due to obesity (mean BMI > 30) and aging.

N Engl J Med. 2024;390:203-211. PMID: 38231621

Testosterone has important benefits to a young man with Klinefelter syndrome and other men with HPT disorders.

T ↑ BMD in men with hypogonadism due to HPT axis disease



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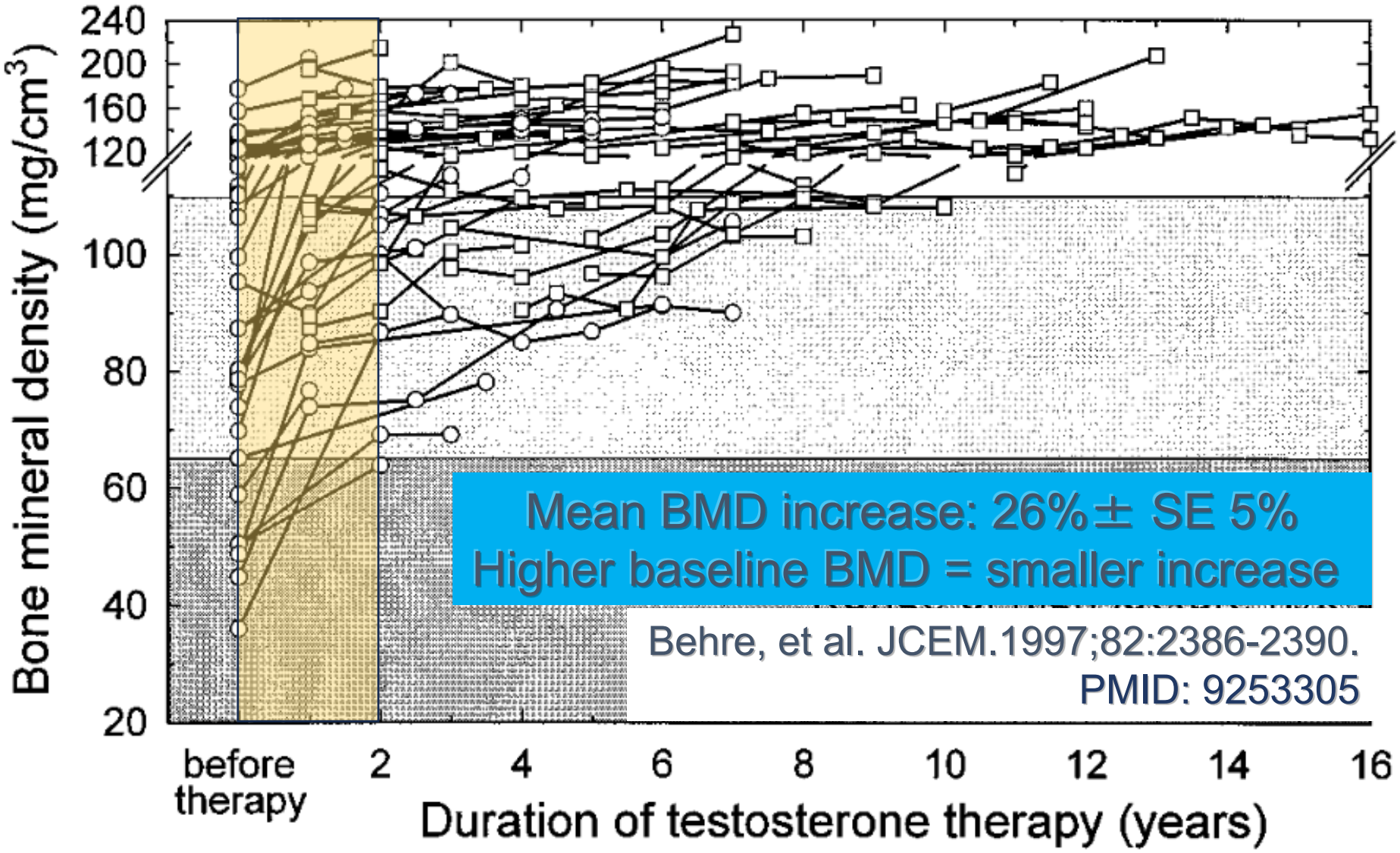
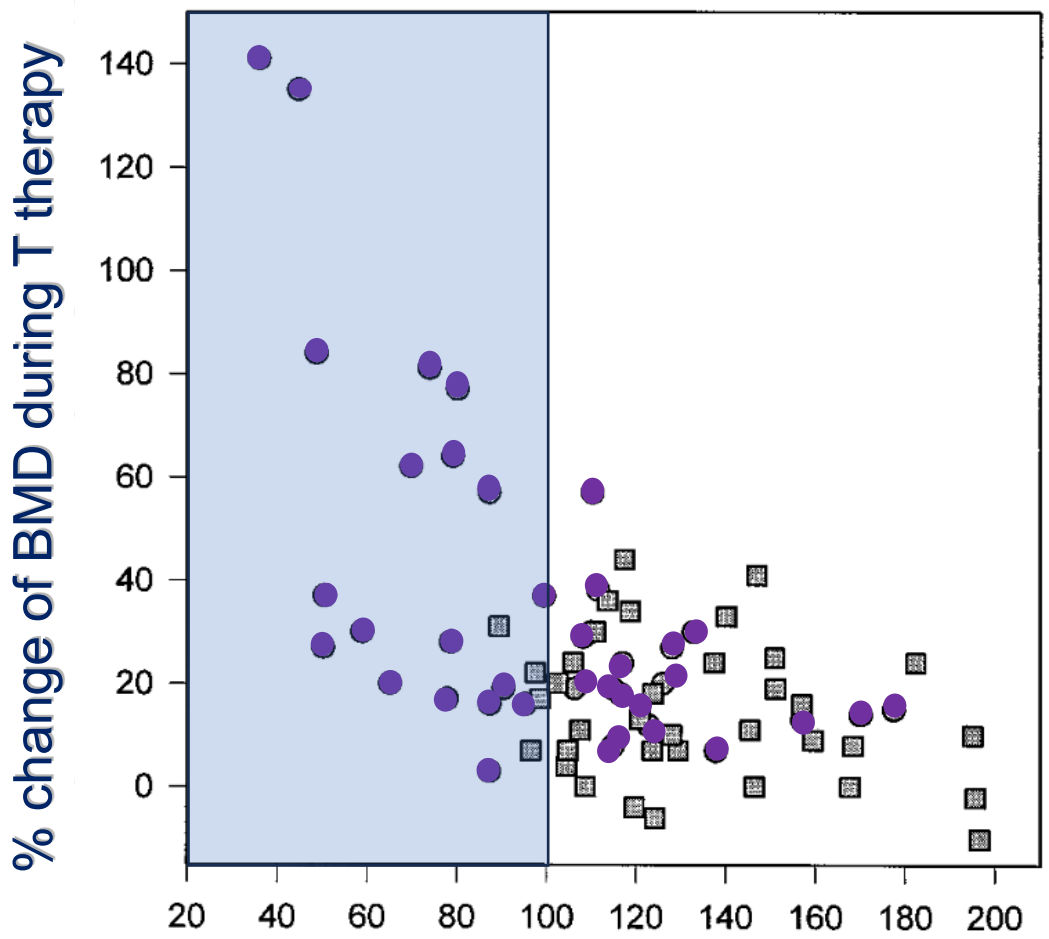


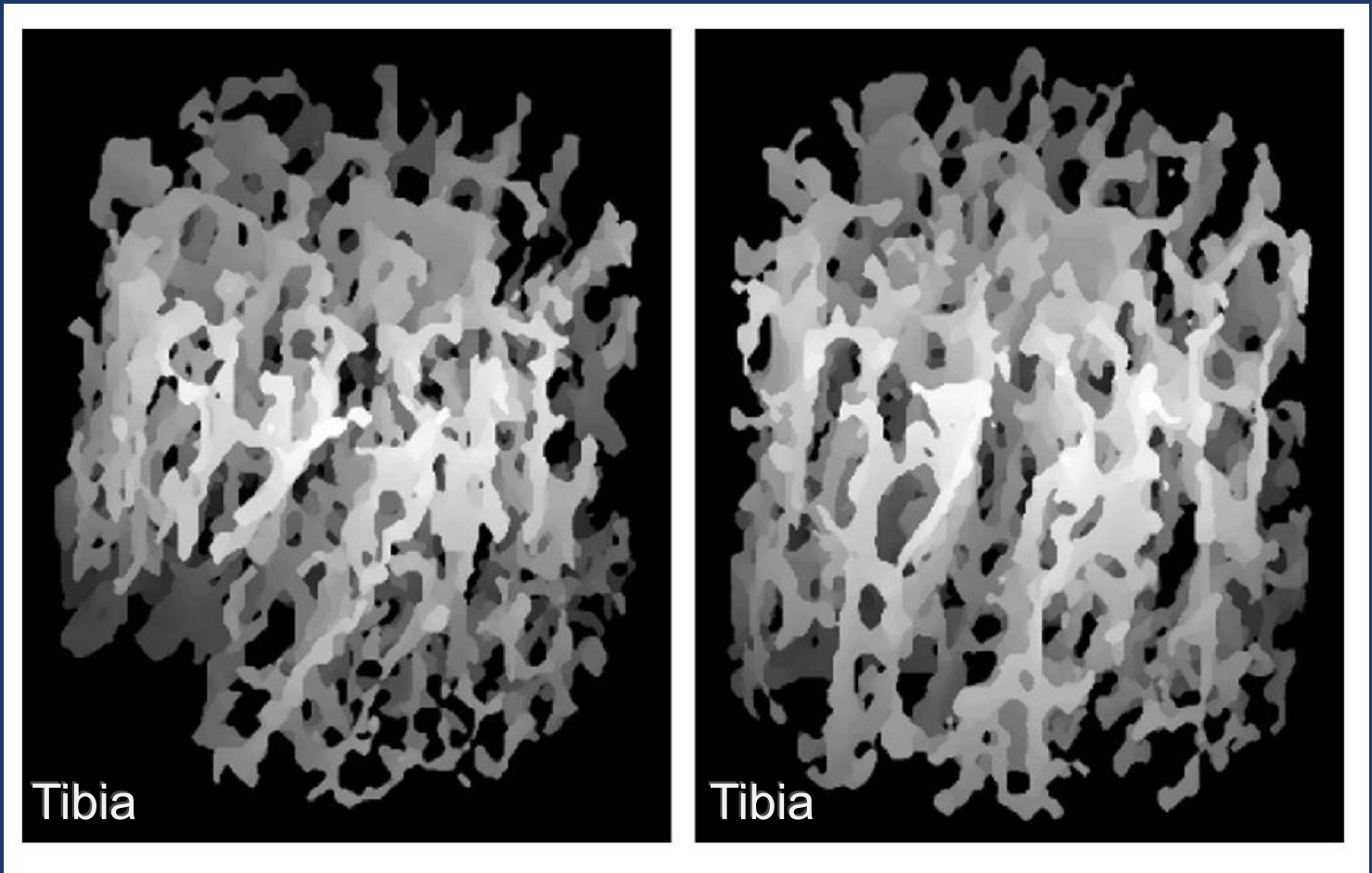
T ↑ areal BMD in men with hypogonadism due to HPT axis disease



Circles = treatment naïve
Square = On T rx at time of first BMD

Behre, et al. JCEM. 1997;82:2386-2390. PMID: 9253305

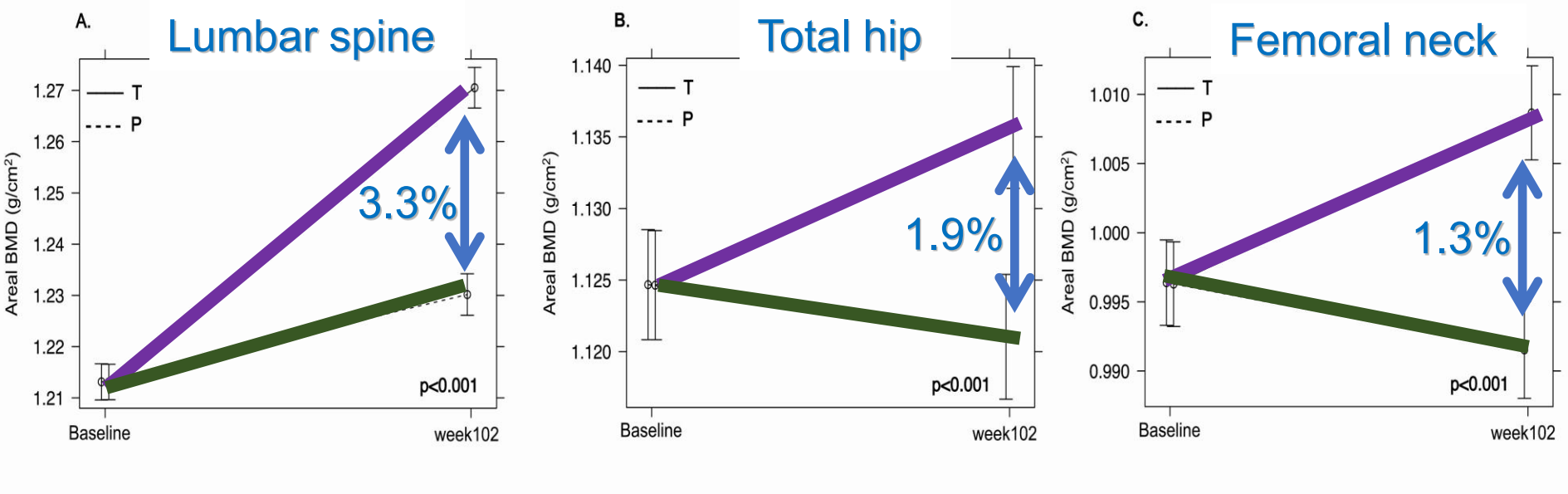
T treatment for 2 yrs increases trabecular bone volume and surface-to-curve ratio and decreased erosion index



10 ♂ with 2º hypogonadism (mean age 51 yrs and total T 88 ng/dL; 3 nmol/L) treated with T gel 1% to increase total serum T to 400-900 ng/dL (13.8-31.25 nmol/L)

Benito, et al. JBMR. 2005;20:1785-1791. PMID: 16160736

T4DM: T ↑ areal BMD (by DXA) in men with hypogonadism without HPT axis disease



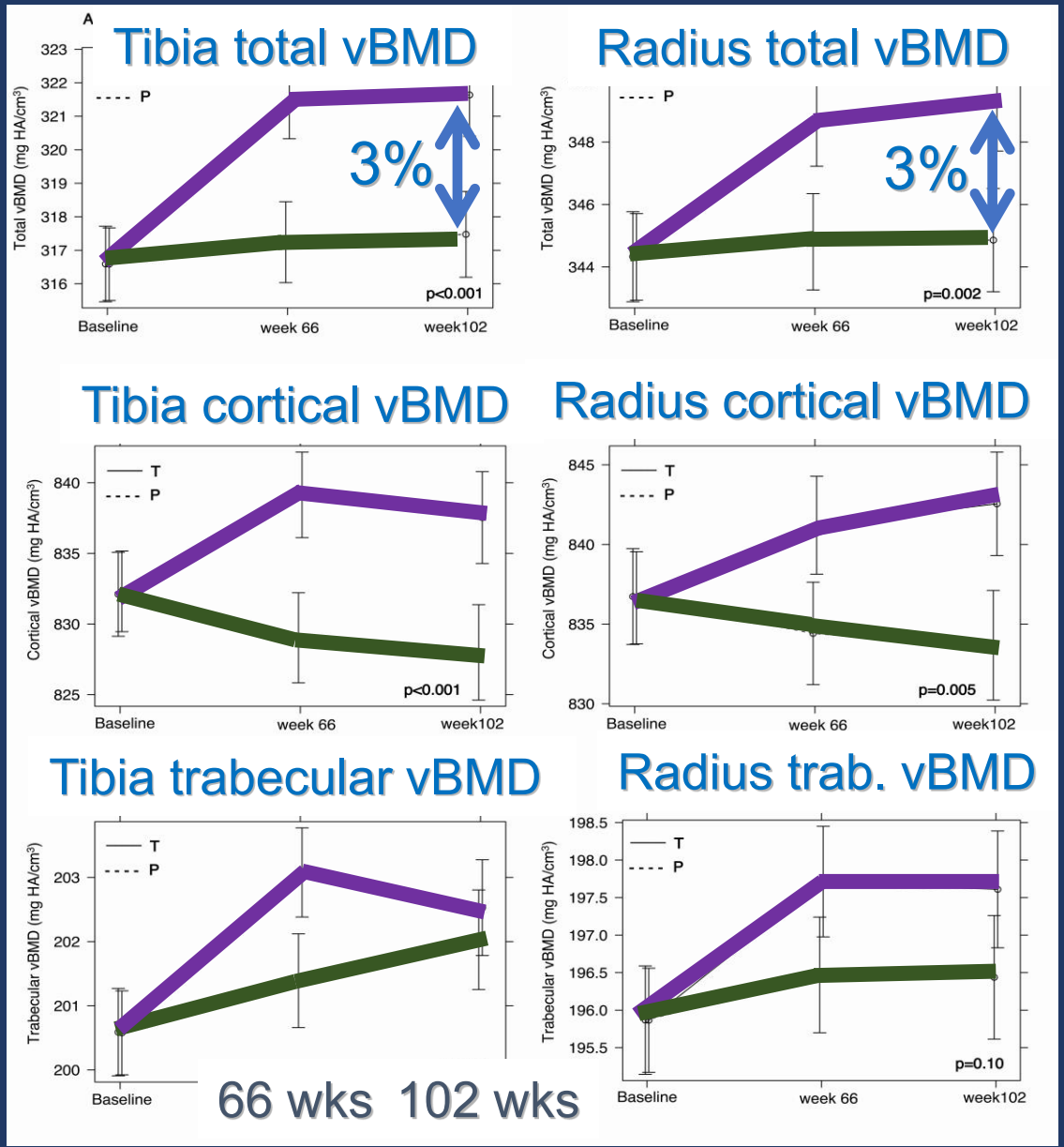
T4Bone study (5 of 6 centers of T4DM)
601 men (50-74 yrs) with serum total T < 404 ng/dL (14 nmol/L) and new DM2 or impaired glucose (oGTT)
Randomized to im testosterone undecanoate 1000 mg q 8 weeks *vs.* placebo

JCEM. 2021;106(8):e3143-e3158.
PMID: 33693907

T4DM: T ↑ volumetric BMD (measured by qCT) in men with hypogonadism without HPT axis

T4Bone study
High-resolution qCT
(n = 177; single center)

P < 0.05
For each Comparison
Except radius Trabecular bone (P=0.10)



Was the right endpoint chosen?

- TRAVERSE: all fractures; no data on trauma

Fracture location	Testosterone (n)	Placebo (n)
Lumbar vertebral	4	2
Thoracic Vertebral	3	4
Hip	6	5
Wrist	11	11
Ribs	17	7
Ankle	12	8
Other	38	28
Total	91	65

TRAVERSE (retrospective) conclusions

- Cohort had low baseline risk of fracture
  - Low total number of fractures
  - No baseline or treatment BMD
  - No baseline fracture data
  - Dosage too low

N Engl J Med. 2024;18;390(3):267-268. PMID: 38231628

- Cohort had low-moderate hypogonadism, and some might have been eugonadal. Mean BMI = 35→low SHBG = low total testosterone, normal free testosterone for many men.
- T dosage was lower than clinical practice and achieved low incremental increase of testosterone from baseline
- No data on T-related behavioral changes regarding activity that might increase fracture risk
- Fracture outcomes dissimilar to other pharmacotherapy trials for osteoporotic fracture prevention

Conclusions: T and bones

- At this time, we cannot recommend testosterone therapy as the sole pharmacological intervention to decrease fractures in hypogonadal men at high 10-year-risk of fracture
- Strong mechanistic evidence to suggest that testosterone treatment decreases fractures in men with HPT axis disease
- Strong mechanistic evidence to suggest that T treatment decreases fractures in men with severe hypogonadism
- No evidence to suggest that T treatment decreases fractures in men with moderate hypogonadism and no HPT axis disease

All 4 recent RCT of T excluded men with HPT disorders

- TEAAM, T-Trials, T4DM, and TRAVERSE
  - Excluded men with HPT disorders
- These studies are useful for identifying adverse T effects for men with mild-moderate hypogonadism without an HPT disorder and likely useful for men with hypogonadism due to classic HPT disorders
- These studies are useful for determining the modest benefits of T treatment to men with mild-moderate hypogonadism but have no classic HPT disease
- These studies likely underestimate the benefits for men with more significant hypogonadism due to classic HPT disease
- The bone data are a good example

Grossmann, Anawalt, Yeap. Testosterone therapy in older men: clinical implications of recent landmark trials. Eur J Endocrinol. 2024;191(1):R22-R31. PMID: 38917356.

Case #2

A 72-year-old man reports declining libido over the past 18 months. He is healthy and lean (waist circumference is 32 inches and BMI 21). He has hypertension and a history of Graves disease in remission.

He has a normal physical exam including testes that 20 cc bilaterally.

Labs:

Serum testosterone	175 ng/dL (264-916 ng/dL)
	6.1 nmol/L (9.2-31.8 nmol/L)
Serum FSH	35.0 mIU/mL (1.0-7.0 mIU/mL)
Serum LH	28.0 mIU/mL (1.0-9.0 mIU/mL)

Case #2

What is the most likely explanation for his laboratory results?

a) Klinefelter syndrome
b) Gonadotropin-secreting pituitary adenoma
c) Clomiphene use
d) Anastrozole use
e) Effects of aging on the testes

Primary hypogonadism increase after age 65

- Labs for 72-year-old man indicate primary hypogonadism
- HIMS study: 1025 men (mean age 75 at baseline)

  0.7% serum total T < 164 ng/dL (6.4 nmol/L) and LH > 12

  7% met the above criteria at 8.6 years of follow-up

  Yeap, et al Clin Endocrinol (Oxf). 2018;1:88-95. doi: PMID: 28945276
- Aging is associated with loss of hypothalamic GnRH neuron and Leydig cell number and/or function. Pituitary gonadotrope function seems to be preserved. Biochemical picture of secondary hypogonadism is most common pattern of aging (and is potentiated by obesity). However, biochemical primary hypogonadism increases significantly starting at age 65-70.
- Consider treatment of men > 65 years who have symptoms and signs of hypogonadism and primary hypogonadism.

  Anawalt and Matsumoto. Rev Endocr Metab Disord. 2022:1123-1137. PMID: 36459352

Case #2

What is the most likely explanation for his laboratory results?

a) ~~Klinefelter syndrome~~ (Small testes, infertility)
b) ~~Gonadotropin secreting pituitary adenoma~~ (RARE)
c) ~~Clomiphene use.~~ Raises serum LH, FSH & T
d) ~~Anastrozole use~~ Raises serum LH, FSH & T
e) Effects of aging on the testes (Usually normal testes and normal fertility)

Case #3

A 58-year-old man requests evaluation for testosterone therapy. He reports that his energy and sex drive are "not what they were when he was 18”. He reports that he infrequently has sexual thoughts and fantasies and has spontaneous morning erections less often than previously. He has a sedentary lifestyle. He take simvastatin for dyslipidemia.

His past medical history is otherwise unremarkable.

Case #3

Physical examination:

Height 69 in (175 cm) BMI = 34 kg/m^2 BP 120/70 mm HR 80

He has a beard. He has 2.5 cm nontender bilateral gynecomastia, and his testes are 20 cc bilaterally.

Labs (drawn at 800 AM, fasting)

Serum testosterone	248 ng/dL (264-916 ng/dL)
	8.6 nmol/L (9.2-31.8 nmol/L)
Serum FSH	4.0 mIU/mL (1.0-7.0 mIU/mL)
Serum LH	2.0 mIU/mL (1.0-9.0 mIU/mL)

Serum prolactin is normal.

Serum T4 and TSH are normal.

Serum iron is normal.

Transferrin saturation is 45% (nl 20-50%).

Sellar MRI (ordered by your colleague while you were on vacation) is normal.

Case #3

Repeat 8 AM (fasting) labs:

Serum testosterone	258 ng/dL (264-916 ng/dL)
	9.0 nmol/L (9.2-31.8 nmol/L)
Serum FSH	3.0 mIU/mL (1.0-7.0 mIU/mL)
Serum LH	4.0 mIU/mL (1.0-9.0 mIU/mL)

Based on the evidence from epidemiological studies, which of the following would be the most useful to help determine whether to initiate testosterone therapy?

a) Free testosterone measured by an accurate method
b) Hemoglobin A1c
c) Bone densitometry by DXA
d) Bone densitometry with trabecular bone score (TBS)
e) Hematocrit

Value of free T measurement

- Accuracy matters
  - Measurement with tandem mass spectrometry after equilibrium dialysis is considered the reference standard
  - Measurement with tandem mass spectrometry after ultrafiltration is also accurate
  - Calculated free T correlates well with measurement with tandem mass spectrometry after equilibrium dialysis

- Two epidemiological studies demonstrate added value of calculated free T based on total T measured by mass spectrometry for the sexual symptoms of hypogonadism

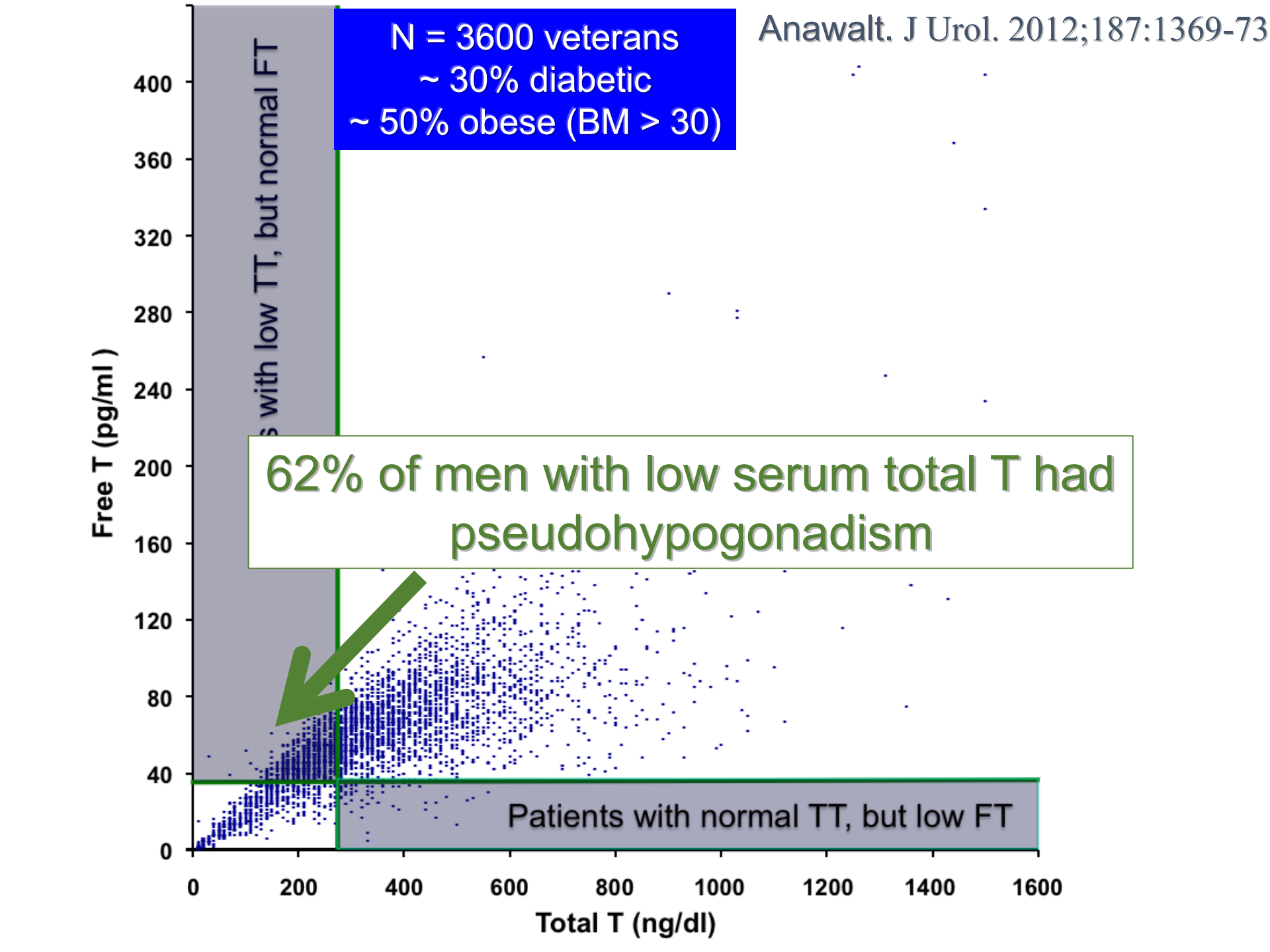
Hsu, et al (CHAMP study). J Gerontol A Biol Sci Med Sci. 2016 ;71:1667-1675. PMID: 26994391

Antonio, et al (EMAS study). J Clin Endocrinol Metab. 2016;101(7):2647-57. PMID: 26909800

Evidence for Free T Hypothesis: CHAMP study

Erectile Dysfunction	Odds ratios	Corrected odds ratios
Normal TT / Normal cFT	**1.00**	**1.00**
Normal TT/ Low cFT	**5.47 (1.65-18.16)**	**4.25 (1.27-14.30)**
Low TT / Normal cFT	0.70 (0.33-1.49)	0.82 (0.38-1.81)
Low TT / Low cFT	**1.47 (1.06-2.02)**	**1.33 (0.95-1.87)**
Low Sexual Satisfaction		
Normal TT / Normal cFT	1.00	1.00
Normal TT/ Low cFT	1.19 (0.35-4.03)	1.03 (0.29-3.57)
Low TT / Normal cFT	1.91 (0.71-5.10)	1.91 (0.64-5.74)
Low TT / Low cFT	**1.95 (1.25-3.03)**	**1.94 (1.22-3.10)**
Low Sexual Desire		
Normal TT/ Normal cFT	1.00	1.00
Normal TT / Low cFT	**3.35 (1.16-9.67)**	2.84 (0.97-8.30)
Low TT / Normal cFT	1.09 (0.51-2.34)	1.16 (0.53-2.53)
Low T T/ Low cFT	**2.20 (1.52-3.20)**	**2.11 (1.42-3.13)**

TT = Total T
cFT= calculated free T


N = 3600 veterans
~ 30% diabetic
~ 50% obese (BM > 30)
Anawalt. J Urol. 2012;187:1369-73
62% of men with low serum total T had pseudohypogonadism
Patients with normal TT, but low FT
Free T (pg/ml)
Total T (ng/dl)
0
40
80
120
160
200
240
280
320
360
400
0
200
400
600
800
1000
1200
1400
1600

Case #3

Repeat 8 AM (fasting) labs:

Serum testosterone	258 ng/dL (264-916 ng/dL)
	9.0 nmol/L (9.2-31.8 nmol/L)
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His calculated free testosterone is low.

Note that the serum total testosterone was measured with a CDC-certified assay!

Do not use a direct (platform) free testosterone assay!

Common causes of hypogonadism

- Primary hypogonadism
  - Klinefelter's syndrome (1:500-1:600)
- Secondary hypogonadism
  - Congenital hypogonadotropic hypogonadism
    Pituitary disease
    - Macroadenomas
    - Iron overload
    - Excessive corticosteroids & opioids
    - Hyperprolactinemia
    - Head and neck radiation
  - Systemic disease (severe)
  - Sleep apnea
- Aging is associated hypogonadism (secondary > primary) – particularly in men with BMI > 30

Thirumalai and Anawalt B. Urol Clin North Am. 2022;49:645-663
Anawalt and Matsumoto, Rev Endo Metab, 2022;23:1123-1137.

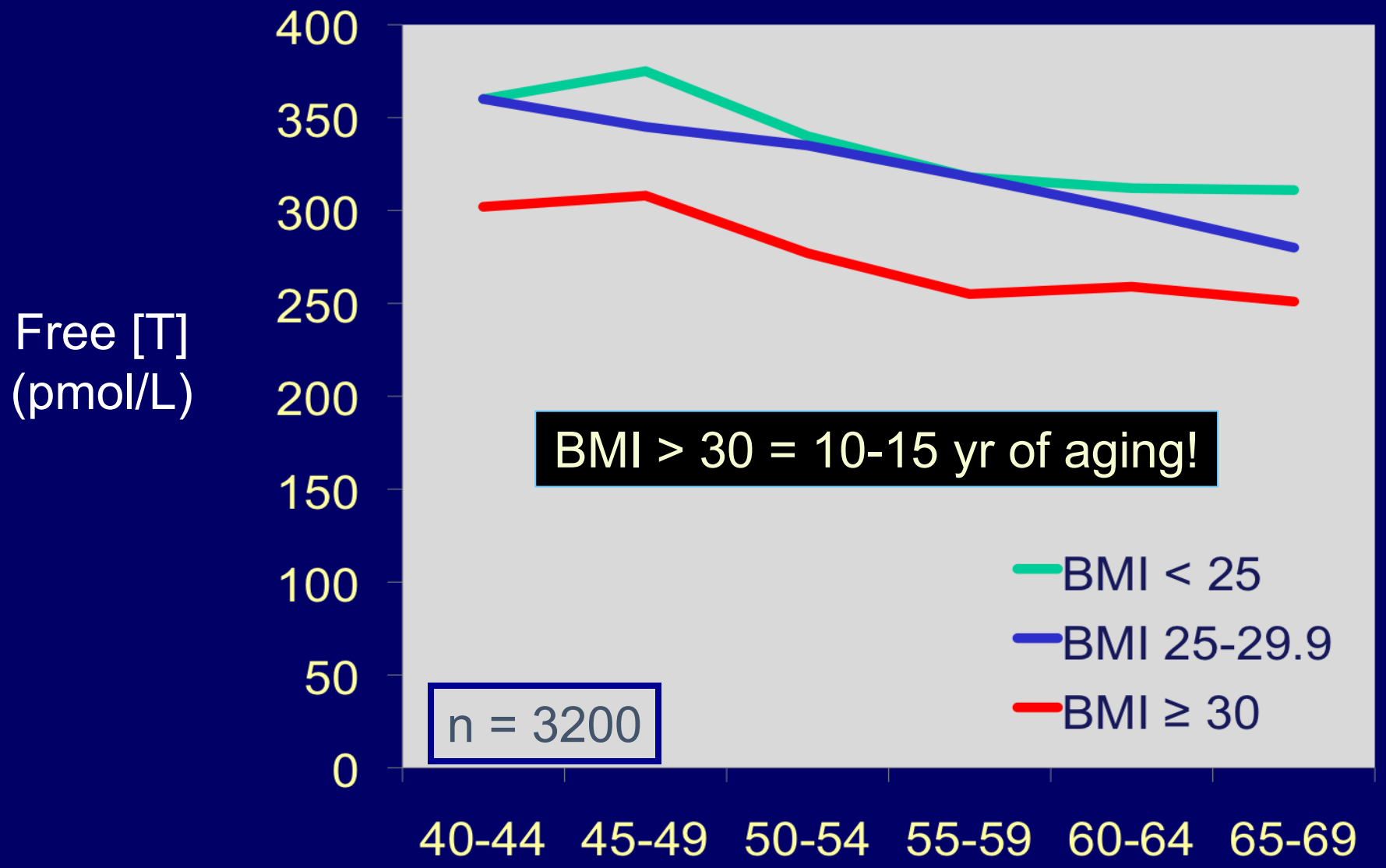
Reversible vs. irreversible hypogonadism

- Irreversible primary hypogonadism
  - Klinefelter's syndrome (1:500-1:600)
- Potentially reversible primary hypogonadism
  - Medications (e.g., high dosage ketoconazole)
- Irreversible secondary hypogonadism
  - Congenital hypogonadotropic hypogonadism*
  - Macroadenomas*
  - Iron overload*
  - Head and neck radiation
- Potentially reversible secondary hypogonadism
  - Excessive corticosteroids & opioids
  - Sleep apnea
  - Obesity/BMI > 30

*Small minority of these condition are reversible

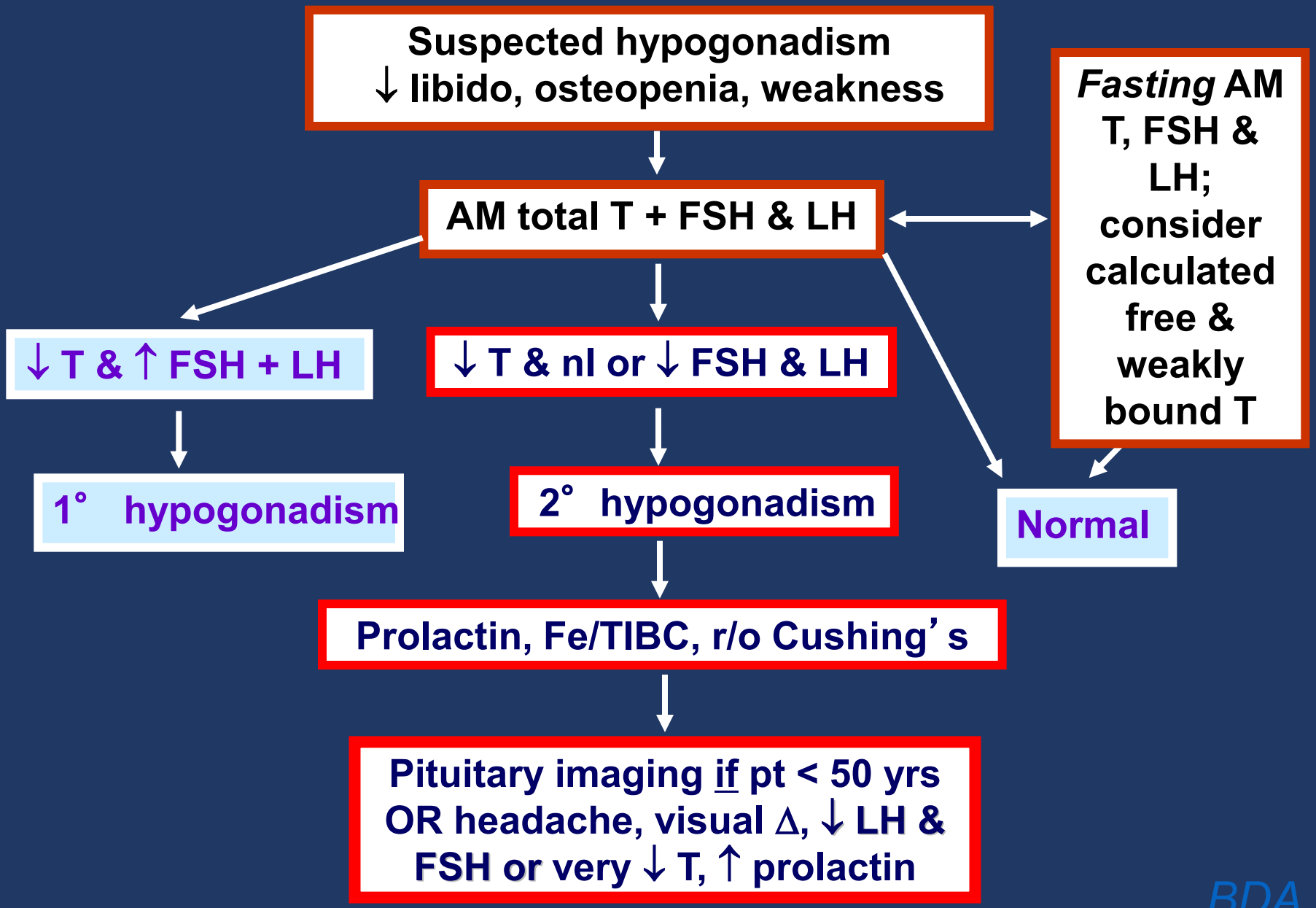
Thirumalai A and Anawalt B. Urol Clin North Am. 2022;49:645-663
Anawalt and Matsumoto, Rev Endo Metab, 2022;23:1123-1137

Obesity & aging synergistically ↓ [T]



J Clin Endocrinol Metab. 2008;93:2737-2745

Hypogonadism algorithm



BDA

Case #3

His calculated free testosterone is 67 pg/mL (LLN 63 pg/mL; 220 pmol/L).

Based on the evidence from placebo-controlled trials, which of the following would be the most useful additional would be most useful in the assessment of potential benefit ?

a) Hemoglobin A1c
b) Bone densitometry by DXA
c) Bone densitometry with trabecular bone score (TBS)
d) Hematocrit
e) PHQ-9

Testosterone therapy and anemia

- Up to 15% of adults > 60 years are anemic and up to 40% of these older adults with anemia have no identifiable cause
- Testosterone Trials
  - ~8% had unexplained anemia at baseline
  - ~60% of those with unexplained anemia corrected with T rx compared to ~ 20% with placebo
- TRAVERSE
  - 16% had baseline unexplained anemia
  - ~40% of these corrected with T rx vs. ~ 25% with PI
  - T rx prevented anemia in ~2-3%
  - Increase of hemoglobin correlated with modest improvement of self-reported energy (HIS-Q)

Alibhai. JAMA Netw Open. 2023;6:e2339969. PMID: 37889494
Pencian, et al. JAMA Netw Open. 2023 O;6:e2340030. PMID: 37889486
Roy, et al. JAMA Intern Med. 2017;177:480-490. PMID: 28241237

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d) Hematocrit
e) PHQ-9

Case #3

Additional history and laboratory information:

His parents and his brother have type 2 diabetes mellitus.

His hematocrit is 43%.

Based on the evidence from epidemiological studies and randomized controlled trials, which of the following is the most likely benefit for this patient?

a) Improved libido
b) Improved erectile function
c) Increased energy
d) Decreased risk of incident type 2 diabetes
e) Improved physical function (e.g., walking speed, stair walking, hand grip strength)

Wu, et al. N Engl J Med. 2010 Jul 8;363(2):123-35. PMID: 20554979

Vitality/ Energy	Mood	Sexual function	Cognitive function	Insulin sensitivity	Diabetes mellitus prevention
↑↑	↑↑	↔↑↑↑	↔↔	↑↑	↑↔

Walking speed	Falls	Chest, hand, leg strength and power	Bone density and strength	Major osteo-porotic fractures	Resolution or prevention of unexplained anaemia
↑	↔	↑↑	↑↑	↔	↑↑

Testosterone therapy and DM2

- Testosterone does not improve A1c in patients with DM2

  Clin Endocrinol (Oxf). 2015;83:344-51
- T4DM: (T treatment to prevent DM2 study)
- Hypothesis: T therapy might revert or delay onset of DM2 in patients with low serum total T and impaired fasting or borderline DM (based on OGTT)
  - 2-year study of over 1000 men with impaired fasting glucose or newly diagnosed DM2 based on OGTT and serum total T < 325 ng/dL (11.3 nmol/L)
  - Everyone enrolled in 2-yr WW interactive program
  - Placebo vs. im TU for 2 years (1000 mg at time 0, 6 weeks, and then q 3 months)
  - 21% placebo had DM2 and 12% of TU group met OGTT criteria for DM2 at 2 years

Wittert, et al. . Lancet Diabetes Endocrinol. 2021;9:32-45. PMID: 33338415

Testosterone therapy and DM2

- Testosterone Trials: T modestly ↑ insulin sensitivity (HOMA-IR) and ↓ serum insulin ($P < 0.05$)
- TRAVERSE showed no significant difference of incident DM2 (13.4% vs 15.8% at 4 years in T and Pl groups).
- Differences between T4DM and TRAVERSE
  - T4DM– all patients with impaired fasting glucose or abnl OGTT
  - TRAVERSE– “prediabetes” = A1c 5.7%-6.4%
    - Many pts with A1c 5.7%-6.0% do not develop DM2
  - Significantly greater T dosage in T4DM
  - Diet and exercise in T4DM
- There might be a small preventive effect or delay in DM2

Lancet Diabetes Endocrinol. 2021;9:32-45. PMID: 33338415

JAMA Intern Med. 2024;184(4):353-362. PMID: 38315466

Eur J Endocrinol, 2024;191:R22-R31. PMID: 38917356

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Case #3

Our patient has the following additional history and labs:
He has mild-to-moderate lower urinary tract symptoms.
No family history of prostate cancer or venous thrombosis.
He has no history suggestive of sleep apnea
Additional laboratory results:
Serum PSA 2.2 ng/dL and repeat hematocrit 42%

Based on the evidence from placebo-controlled trials, which of the following is the most likely harm of transdermal testosterone therapy for this patient?

a) Urinary obstruction
b) Serum PSA > 4.0 ng/dL
c) Idiopathic venous thrombosis
d) Erythrocytosis
e) Major adverse cardiovascular event (MI, stroke)

Testosterone therapy and prostatic effects

- Observational studies have shown no relationship between testosterone therapy and incident BPH/LUTS or CaP.
- Small studies have shown possible improvement of LUTS
- Placebo-controlled RCTs
  - Did not include men with severe LUTS or high risk of CaP
  - No difference in LUTS
    - Possible small absolute increase of urinary retention
  - PSA typically increases by 0.2-0.5 ng/mL
    - ~ 5% PSA increase > 1.7
    - 2.5% PSA increase > 3.4 ng/mL
  - Low incidence of CaP that did not differ from placebo

LUTS = lower urinary tract symptoms CaP = prostate cancer

Grossman, Anawalt, Yeap. Eur J Endocrinol, 2024;191:R22-R31.
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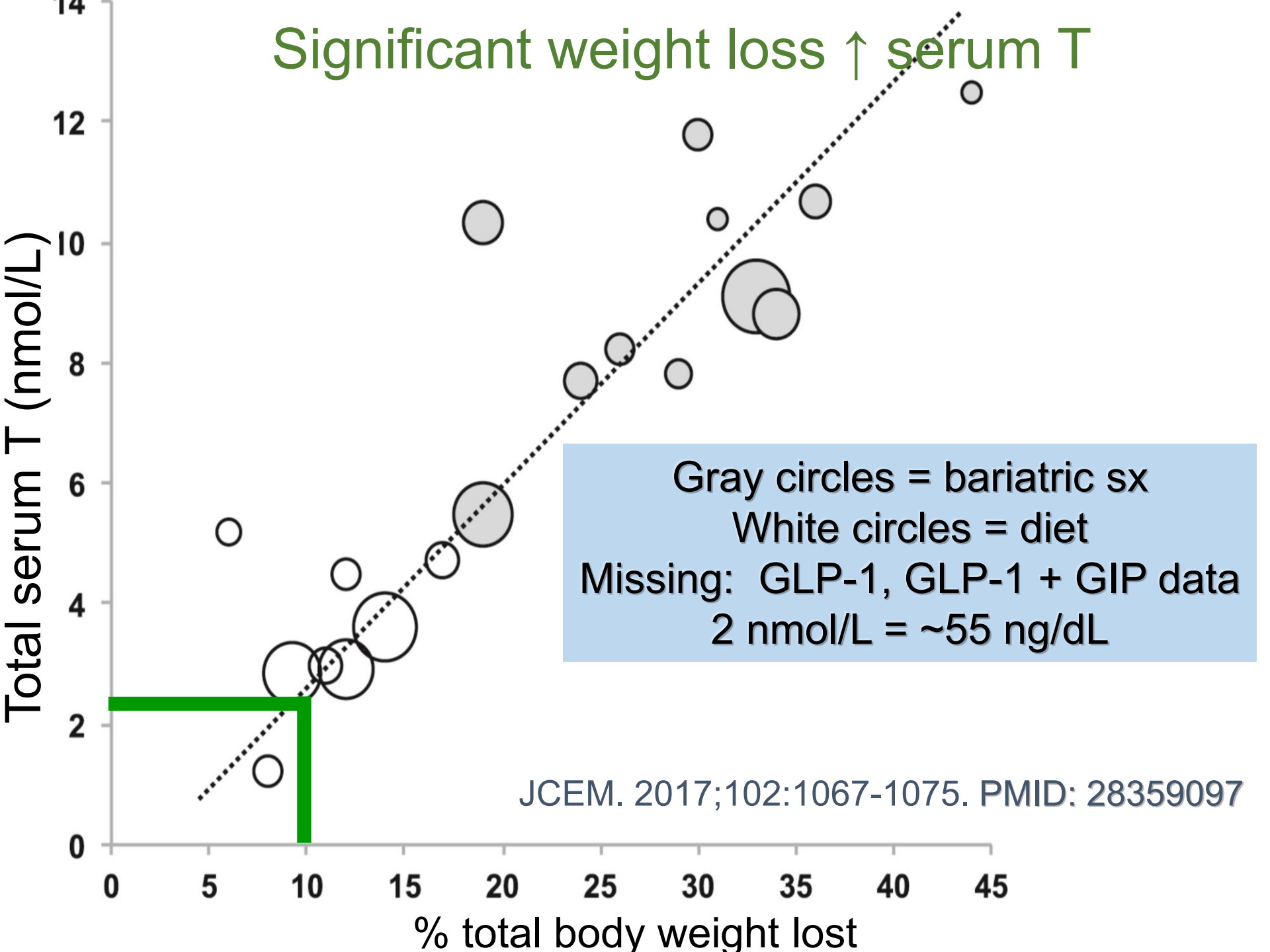
c) Idiopathic venous thrombosis
d) Erythrocytosis
e) Major adverse cardiovascular event (MI, stroke)

Case #3

Our patient is anxious about the small potential risk of pulmonary embolism and does not want start testosterone. He also saw on Reddit that a study showed that men who were on testosterone therapy. He enquires about what else he can do.

Significant weight loss ↑ serum T



JCEM. 2017;102:1067-1075. PMID: 28359097

Management of reversible 2º hypogonadism due to obesity and aging

- Increase exercise (≥150 minutes weekly)
- Healthy diet
  - Avoid foods with nutrition labels
  - Avoid foods with sugar in first 3 ingredients
- Goal of decreased waist size and weight loss of 5-10%
- Avoid (and stop) medications that ↓ serum LH and T
  - Corticosteroids
  - Opioids
  - Drugs that raise serum prolactin
- Consider assessment for sleep apnea

Conclusions

- Men with hypogonadism due to HPT disease are more likely to have significant benefit from exogenous T
- Men with BMI > 27 and hypogonadism without HPT disease may revert to eugonadism with lifestyle changes and improved health
  - For these men, absence of sexual symptoms (i.e., decline of libido), borderline low or low serum T, or normal free T are indications for lifestyle intervenitons first.
  - For these men, sexual symptoms and unexplained anemia have the strongest evidence for exogenous T
  - Fracture prevention, physical function, and DM2 prevention deserve further study

4 major clinical testosterone outcomes trials since 2016

TEAAM 2017	N= 308 ≥60 years Serum total T 100-400 ng/dL	T 75 mg transdermal gel vs. placebo gel daily for 3 years	Carotid artery intimal thickness and coronary artery calcium scores
T-Trials 2016	N = 790 ≥65 years Serum total T ≤275 ng/dL + symptoms or signs of T deficiency	T 50 mg transdermal gel vs. placebo gel daily with dosage adjusted to keep the serum T concentration within normal range for 1 year	Seven sub-studies with different primary outcomes

T4DM 2021	N = 1007 50–74 years Serum total T ≤404 ng/dL Impaired glucose tolerance or newly dx'd DM2 by oral glucose tolerance test	Intramuscular T undecanoate 1000 mg vs. placebo at 0 weeks and 6 weeks, then every 3 months for 2 years + Weight Watchers (WW)	Prevention or reversion of type 2 diabetes as defined by a end-of-treatment serum oral glucose tolerance test
TRA-VERSE 2023	N = 5246 45–80 years Serum total T 100-300 ng/dL + symptoms or signs of T deficiency	T gel with dosage adjusted to maintain serum total T concentrations between 12.1 nmol/L and 26.0 nmol/L and to maintain a haematocrit of ≤54%) vs. placebo gel daily up to 4 years (mean = 22	Composite of major cardiovascular adverse event (non-fatal myocardial infarction, non-fatal stroke, or cardiovascular-related death)

Vitality/ Energy	Mood	Sexual function	Cognitive function	Insulin sensitivity	Diabetes mellitus prevention
↑↑	↑↑	↔↑↑↑	↔↔	↑↑	↑↔

Walking speed	Falls	Chest, hand, leg strength and power	Bone density and strength	Major osteo-porotic fractures	Resolution or prevention of unexplained anaemia
↑	↔	↑↑	↑↑	↔	↑↑

MACE*	VTE*	Pulmonary embolism	↑ PSA > 4 (increasing CaP assessment)
↔ ↔ ↔ ↔	↔ ↔ ↔ ↔	↑?	↑↑
BPH with lower urinary tract symptoms	**Urinary retention**	**Overall fractures**	**Erythrocytosis**
↑?	↑?	↑	↑↑↑↑