Andropause:
When is testosterone indicated

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Andropause

- The decline in testosterone levels associated with signs and symptoms of androgen deficiency

Disagreements & Synonyms

- Partial Androgen Deficiency of the Aging Male(PADAM)

- Androgen Decline in the Ageing Male(ADAM)

- Ageing Male Syndrome(AMS)

- Male Menopause

- Male Climacteric

- Late Onset Hypogonadism(LOH)

Aging males and Testosterone
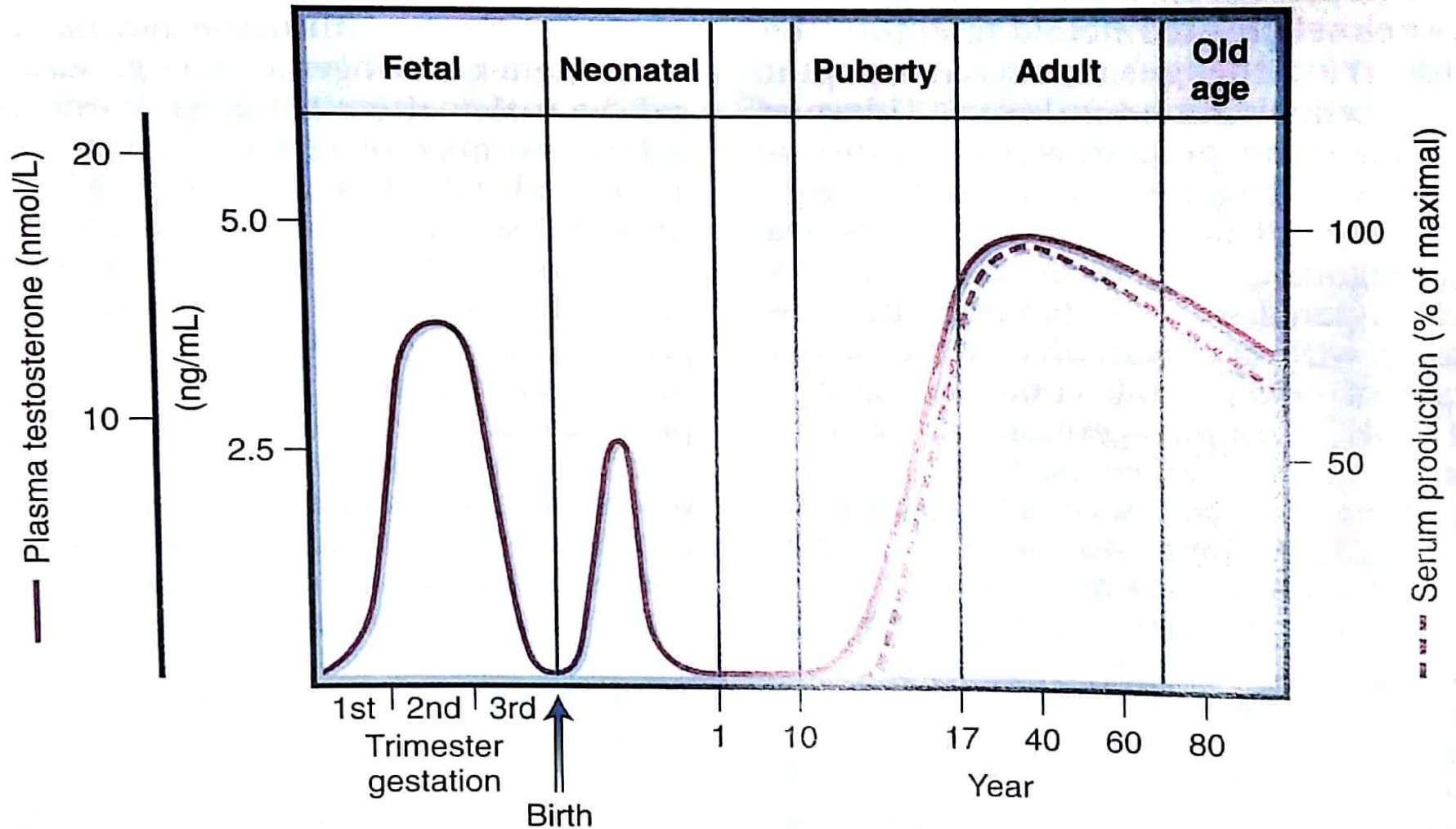
♂ The dotted line is sperm production
♂ The straight line is plasma testosterone level

Male counterpart of Menopause?

- Probably not

- True andropause exists only in those men who have lost testicular function due to diseases, accidents or surgery

Low Serum Testosterone Level

What Is Considered to Be a Low Serum Testosterone Level?

- Total Testosterone <300 ng/dL*
- Free Testosterone <50 pg/mL
- Bioavailable Testosterone <70 ng/dL

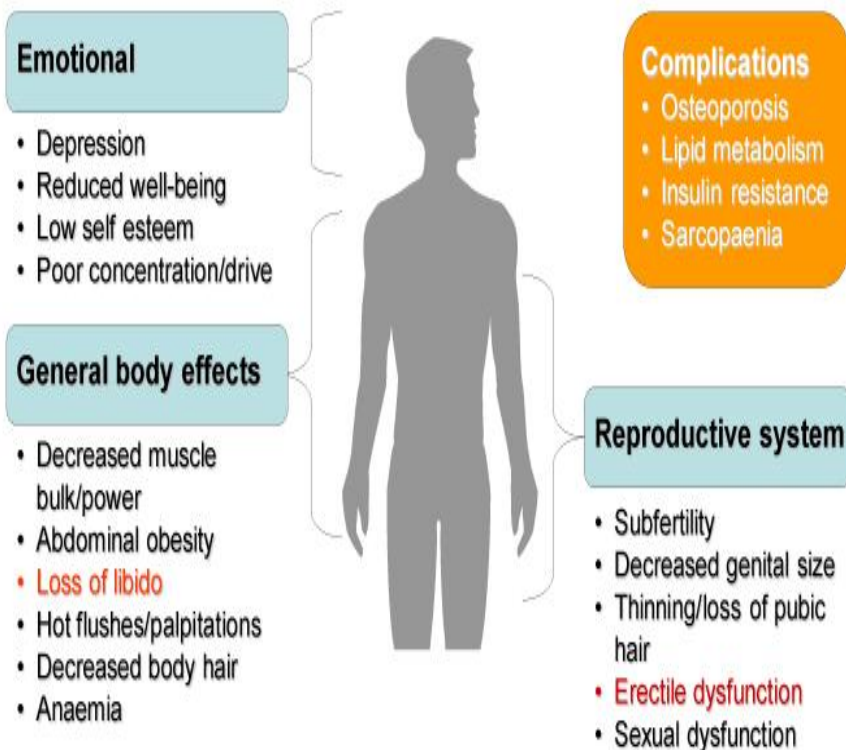*Total testosterone is the most frequently used laboratory test for the diagnosis of hypogonadism in the medical literature*

Brawer MK. Rev Urol. 2004;6 suppl 6:S9-S15.
AACE Hypogonadism Task Force. Endocr Pract. 2002;8:439-456.

Prevalence

- ~24% by Araujo et al.

- Increases with age

Clinical Feature

Clinical picture of testosterone deficiency[1]

Emotional
- Depression
- Reduced well-being
- Low self esteem
- Poor concentration/drive

General body effects
- Decreased muscle bulk/power
- Abdominal obesity
- Loss of libido
- Hot flushes/palpitations
- Decreased body hair
- Anaemia

Complications
- Osteoporosis
- Lipid metabolism
- Insulin resistance
- Sarcopaenia

Reproductive system
- Subfertility
- Decreased genital size
- Thinning/loss of pubic hair
- Erectile dysfunction
- Sexual dysfunction

1. Nieschlag E and Behre HM. Testosterone action deficiency, substitution (3rd Edition). Cambridge University Press, 2004

SYMPTOMS OF TESTOSTERONE DEFICIENCY

Q What symptoms are characteristic of testosterone deficiency?

Degree of Deficiency — Mild → Severe

- Decreased libido
- Decreased vitality
- Fatigue
- Mood changes
- Insomnia
- Anemia
- Delayed ejaculation
- Flushes
- Erectile dysfunction
- Decreased muscle mass
- Increased visceral body fat
- Testicular atrophy
- Weakness
- Osteopenia/osteoporosis
- Loss of facial, axillary and pubic hair

1. Morales et al. CUAJ. 2010;4:269-75; 2. Bhasin et al. J Clin Endocrinol Metab. 2010;95:2536-59.

HOME

Low Testosterone and Symptoms

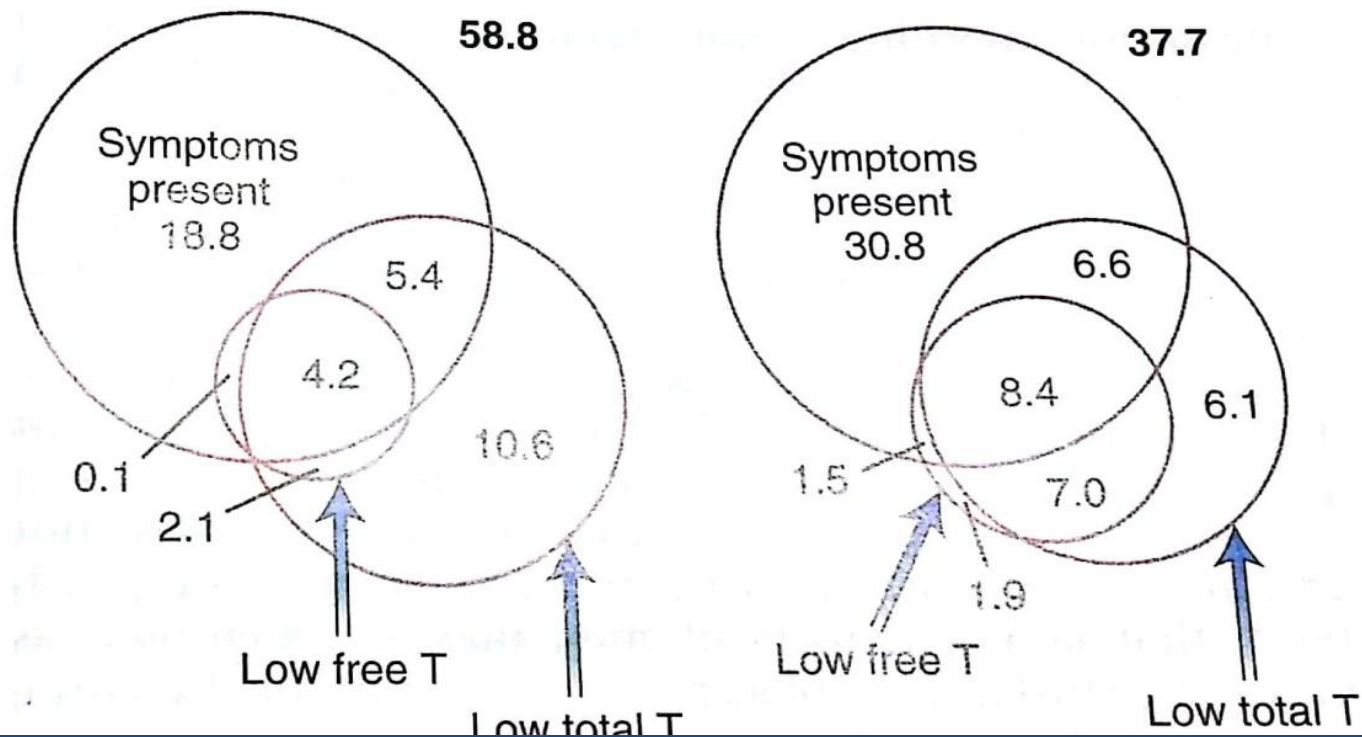- **Variable**

- **Overlapping**

- **Nonspecific**

The Study on epidemiology Araujo et al.

- Low libido, Erectile dysfunction, Osteoporosis
- And any of the two following:
- Sleep disturbance
- Depressed mood
- Lethargy

- Diminished Physical performance **with**
- Total Testosterone < 10.4 nmol/L(300ng/dL), and Free Testosterone < .17 nmol/L(30pg/mL)

Overlaps between symptoms and Low Testosterone

I226   ENDOCRINOLOGY AND AGING

58.8   37.7

Symptoms present 18.8

5.4

4.2

0.1

2.1

10.6

Low free T

Low total T

Symptoms present 30.8

6.6

8.4   6.1

1.5

7.0

1.9

Low free T

Low total T

Symptoms with Low Testosterone are commoner in >50 yrs (Right van diagram)

BEYOND FORTY

- The available studies Demonstrate:

- Slow decline in testosterone production
- Individual variation
- Androgens are affected by comorbidities
- No significant change

This Less Studied Area are being Enriched by Recent Studies

Aging Males and Testicular function

Age-related Decline in Testicular Function
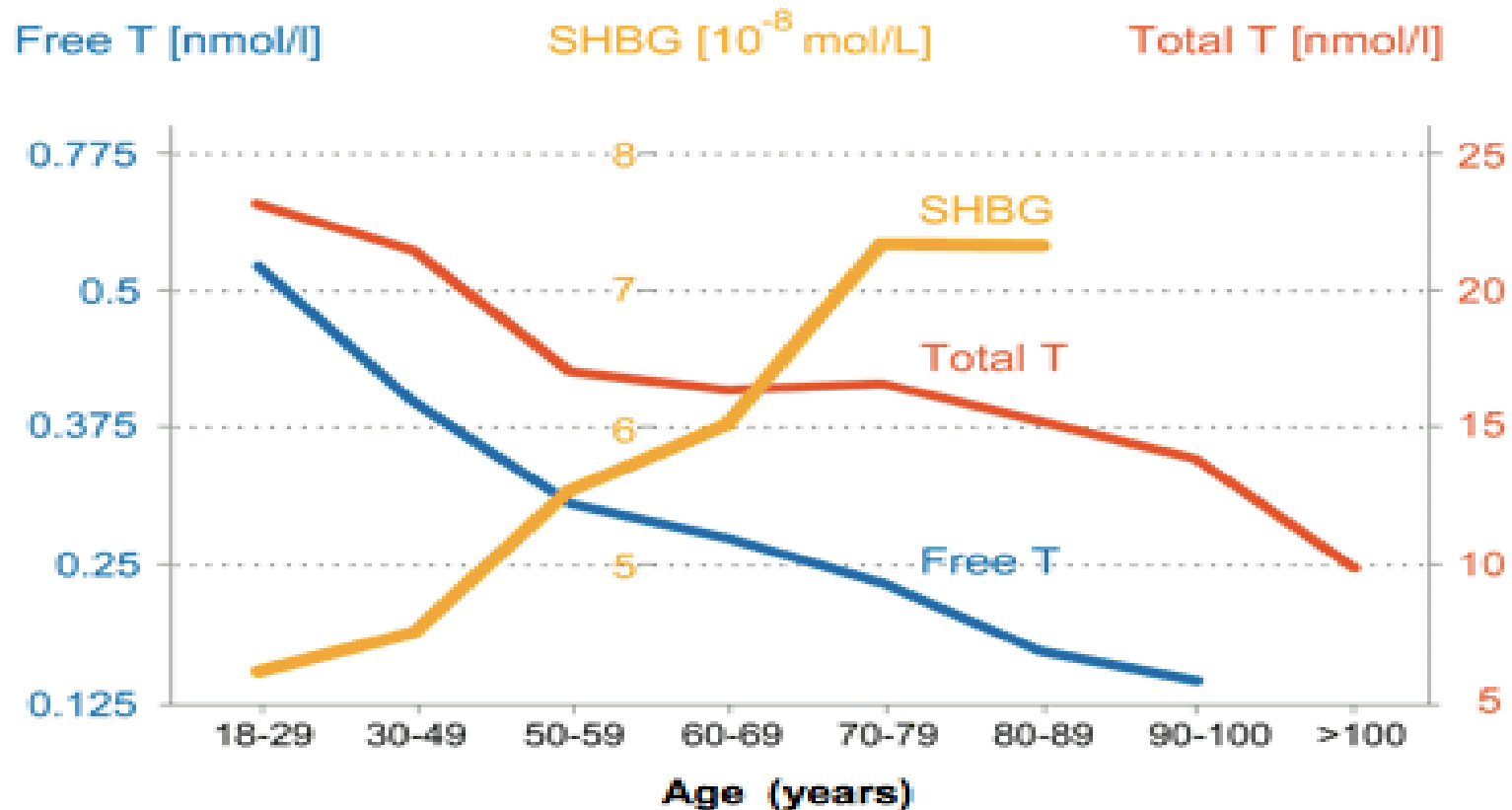
The decline in total testosterone (T) level is evident from the age of 45–50 years.
Free (bioavailable) testosterone starts to decline even earlier due to increasing levels of sex hormone–binding globulin (SHBG) which binds tightly to testosterone.
Data from Vermeulen A. 1993 Annals of Medicine 25:531–4
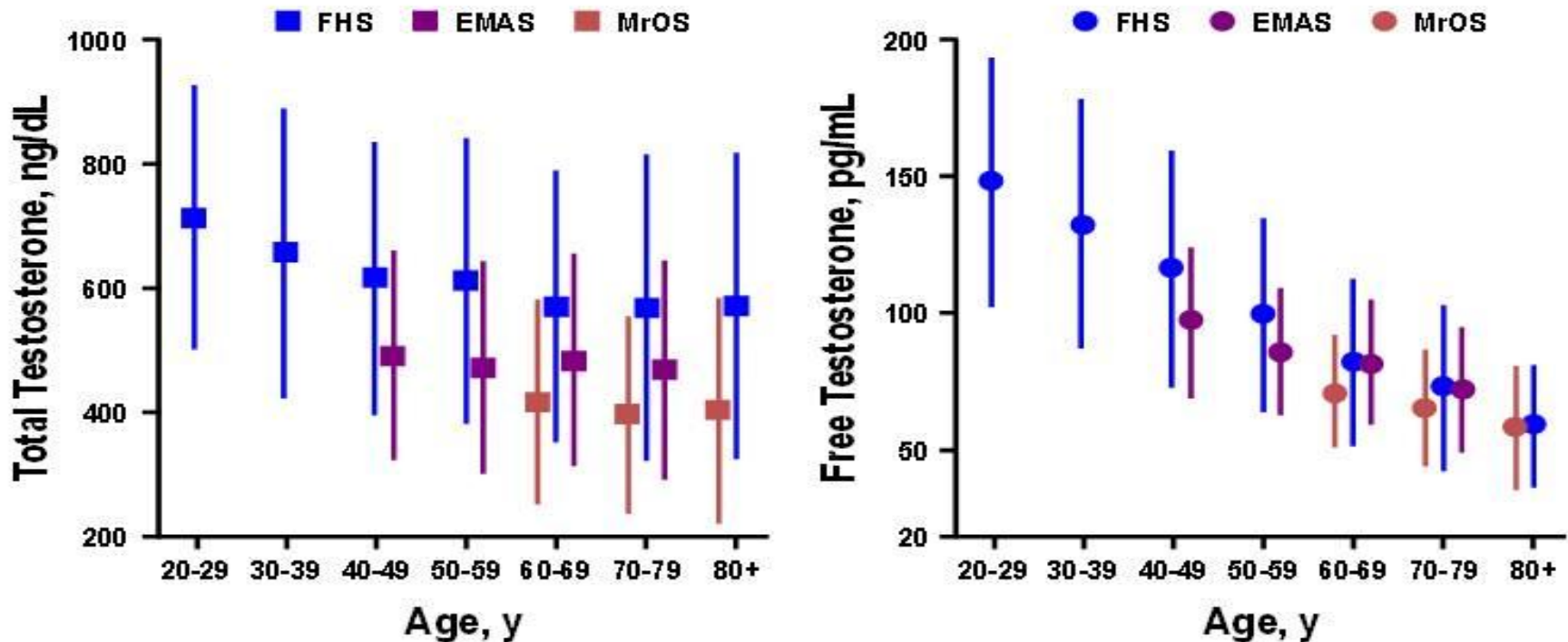
Testosterone Levels
Age-related Changes
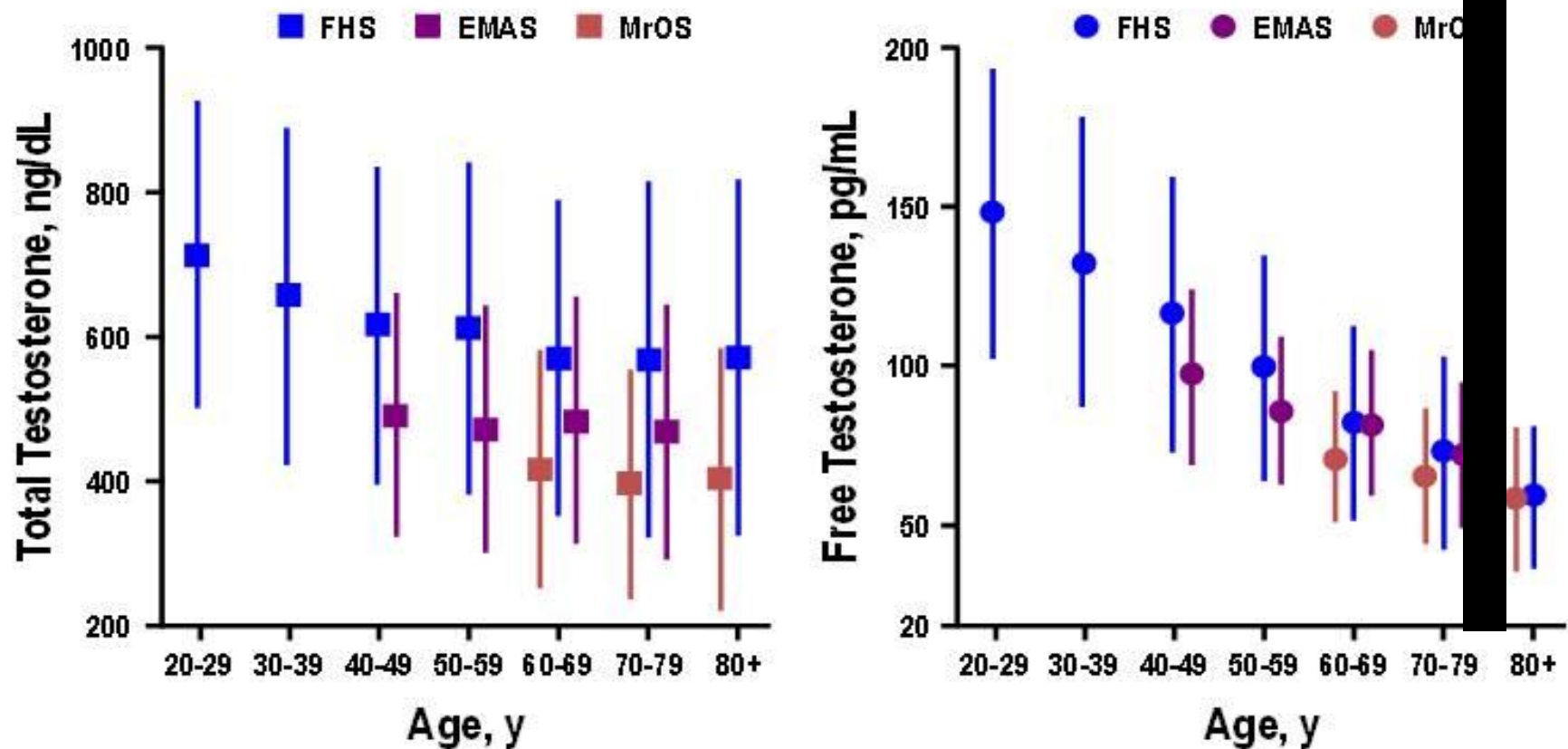
EMAS, European Aging Male Study; FHS, Framingham Heart Study; MrOS, Osteoporotic Fractures in Men Study.
Bhasin S, et al. *J Clin Endocrinol Metab.* 2011;96(8):2430-2439.
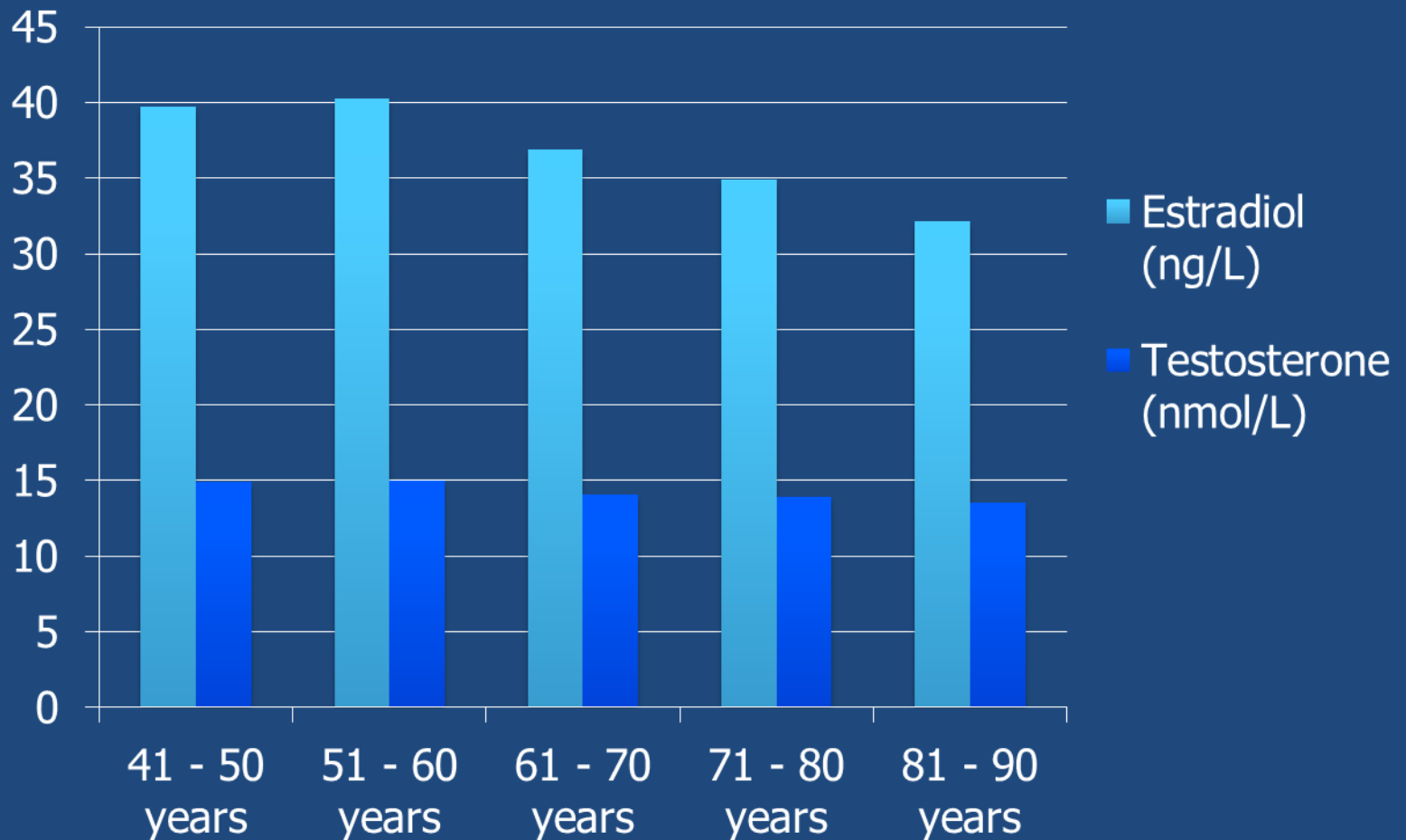
Aging Males and Testosterone level

## Testosterone Levels
Age-related Changes

EMAS, European Aging Male Study; FHS, Framingham Heart Study; MrOS, Osteoporotic Fractures in Men Study.
Bhasin S, et al. *J Clin Endocrinol Metab*. 2011;96(8):2430-2439.

Gonadal Hormones & Gonadotrophins in healthy males beyond forty years
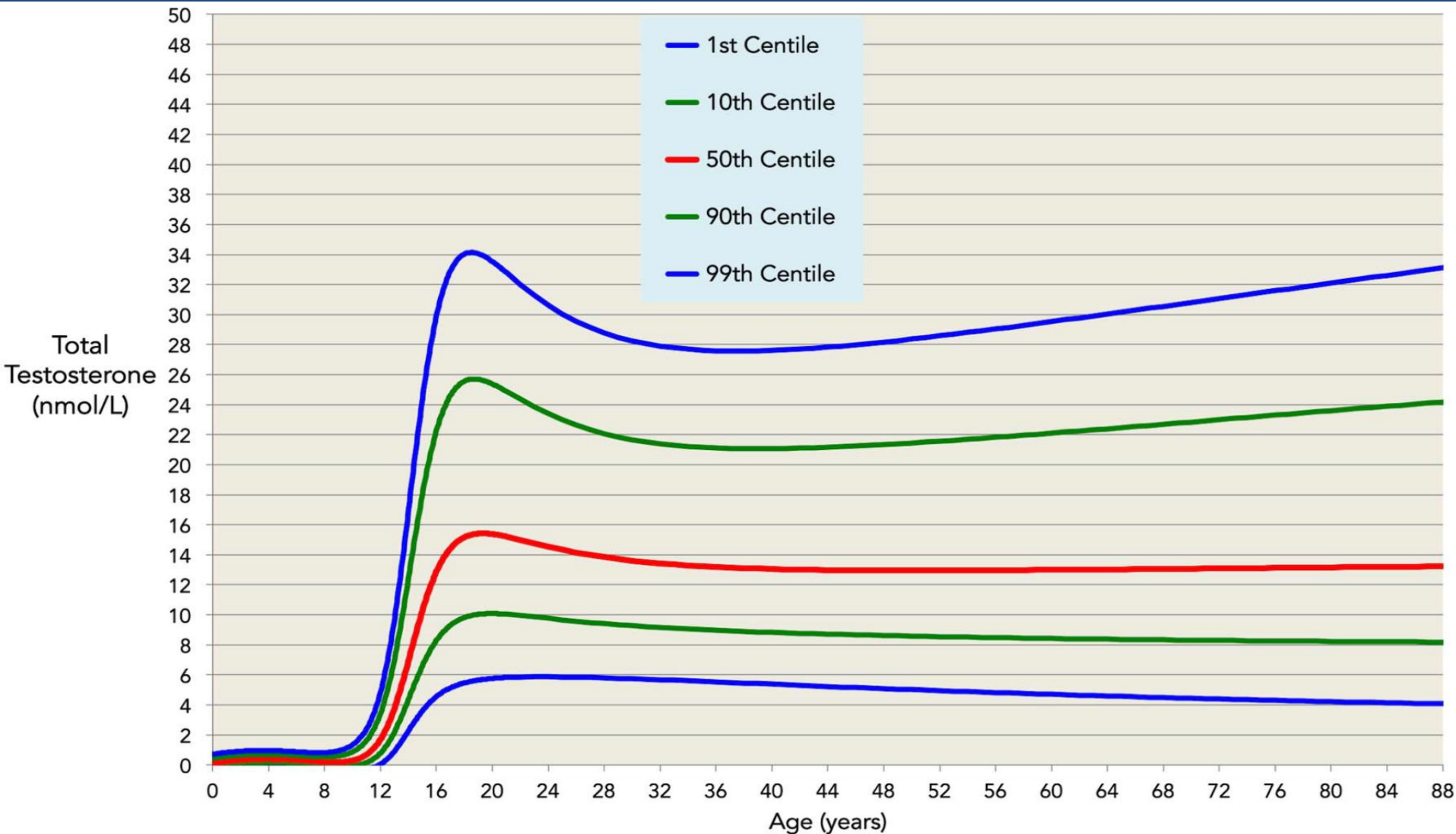## Ansari AJ et al. JPMA:56:203;2006

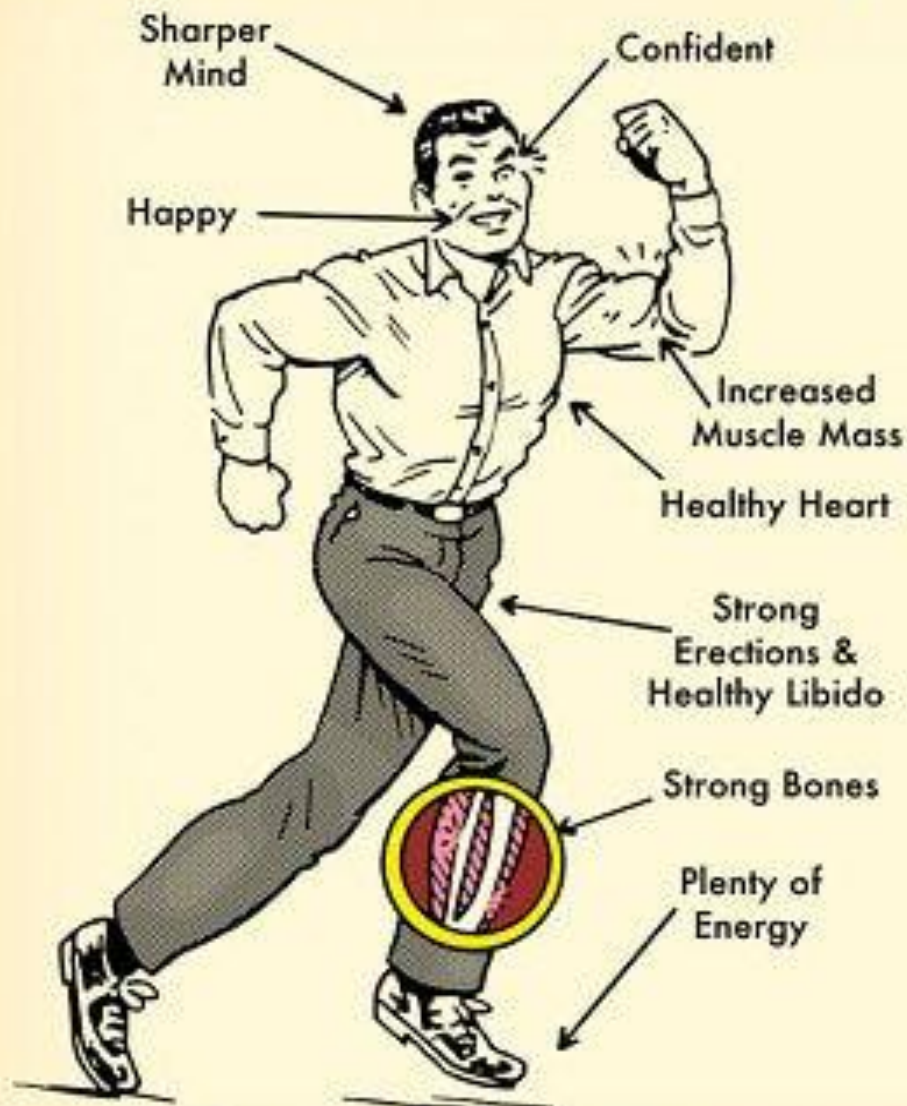# Serum Testosterone Level Changes With Age: The Mean Variations
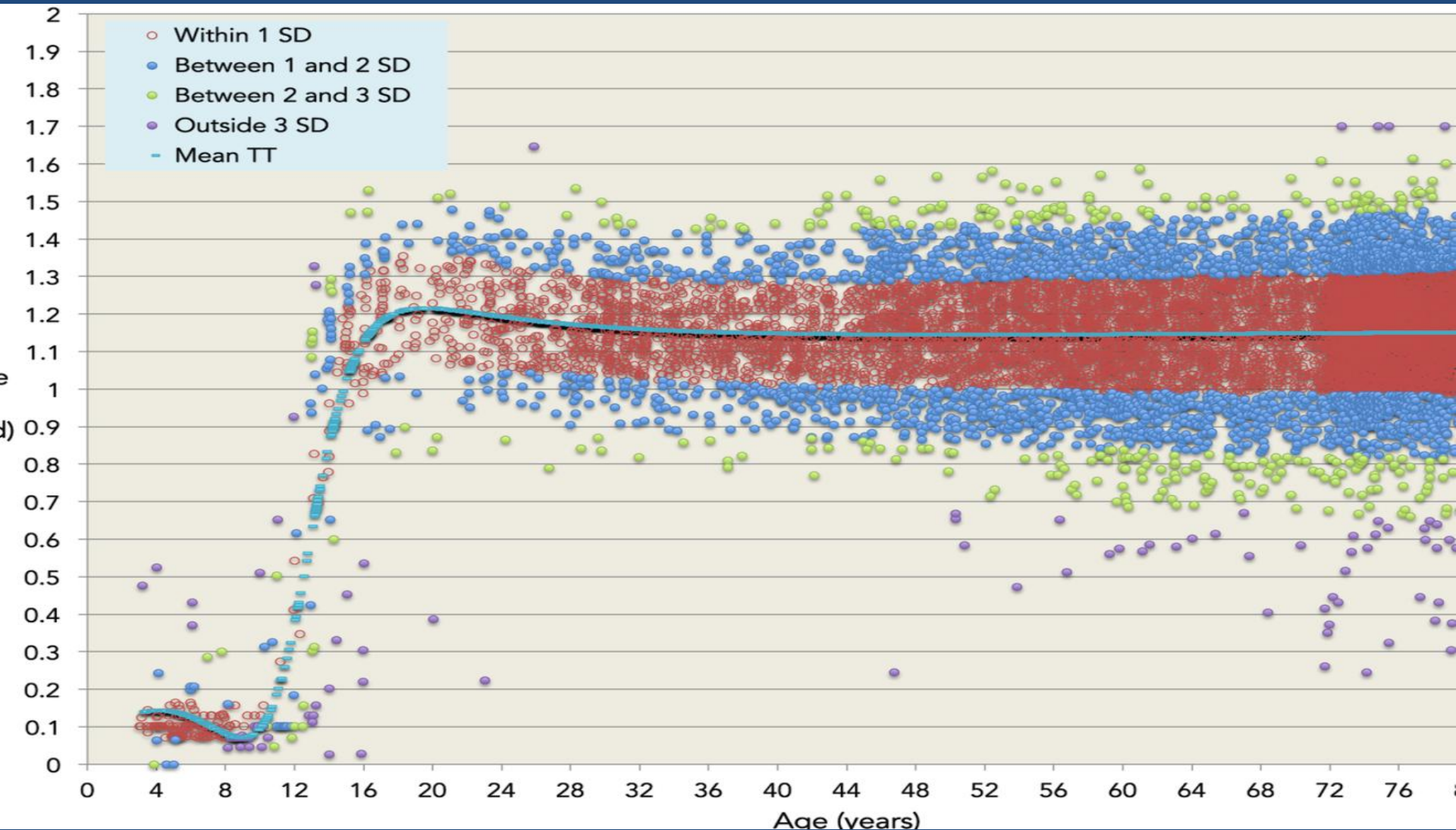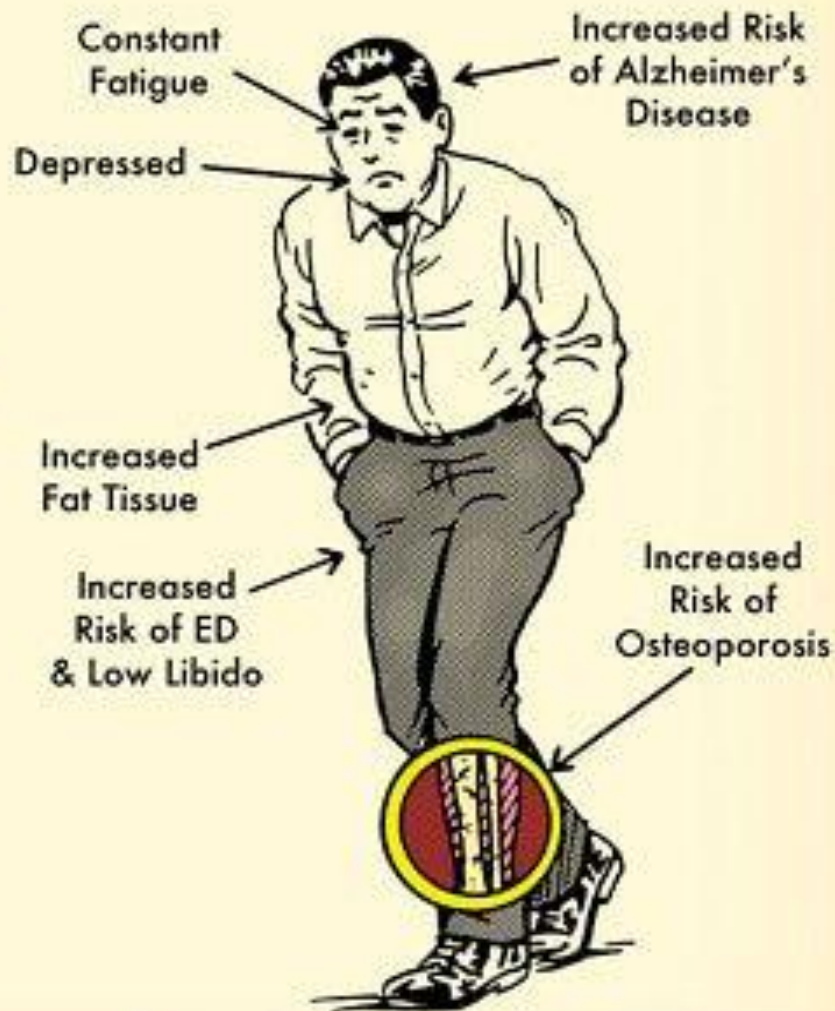
Decide which percentile

In conclusion, This model provides the reference ranges needed to support research and clinical decision making in males who have symptoms that may be due to hypogonadism. In addition, our study suggests that instead of a gradual decline in testosterone levels in men as they age there is an increasing variation in testosterone levels in aged men with a larger population of hypogonadal males, who may benefit from testosterone therapy, but also more men with high serum total testosterone that may also be disadvantageous [56].

- A significant number of elderly males are androgen deficient and symptomatic

- Do they get benefit by Replacement
- Expectations from replacement
- Scientific evidences

The Benefits of Optimal Testosterone

Sharper Mind

Confident

Happy

Increased Muscle Mass

Healthy Heart

Strong Erections & Healthy Libido

Strong Bones

Plenty of Energy

Man with Optimal Testosterone

Constant Fatigue

Increased Risk of Alzheimer's Disease

Depressed

Increased Fat Tissue

Increased Risk of ED & Low Libido

Increased Risk of Osteoporosis

Man with Deficient Testosterone

The Art of
MANLINESS

Benefits of sexual activity

A Sexual Activity

Change from Baseline in PDQ–Q4 Score vs Month

P<0.001

Testosterone
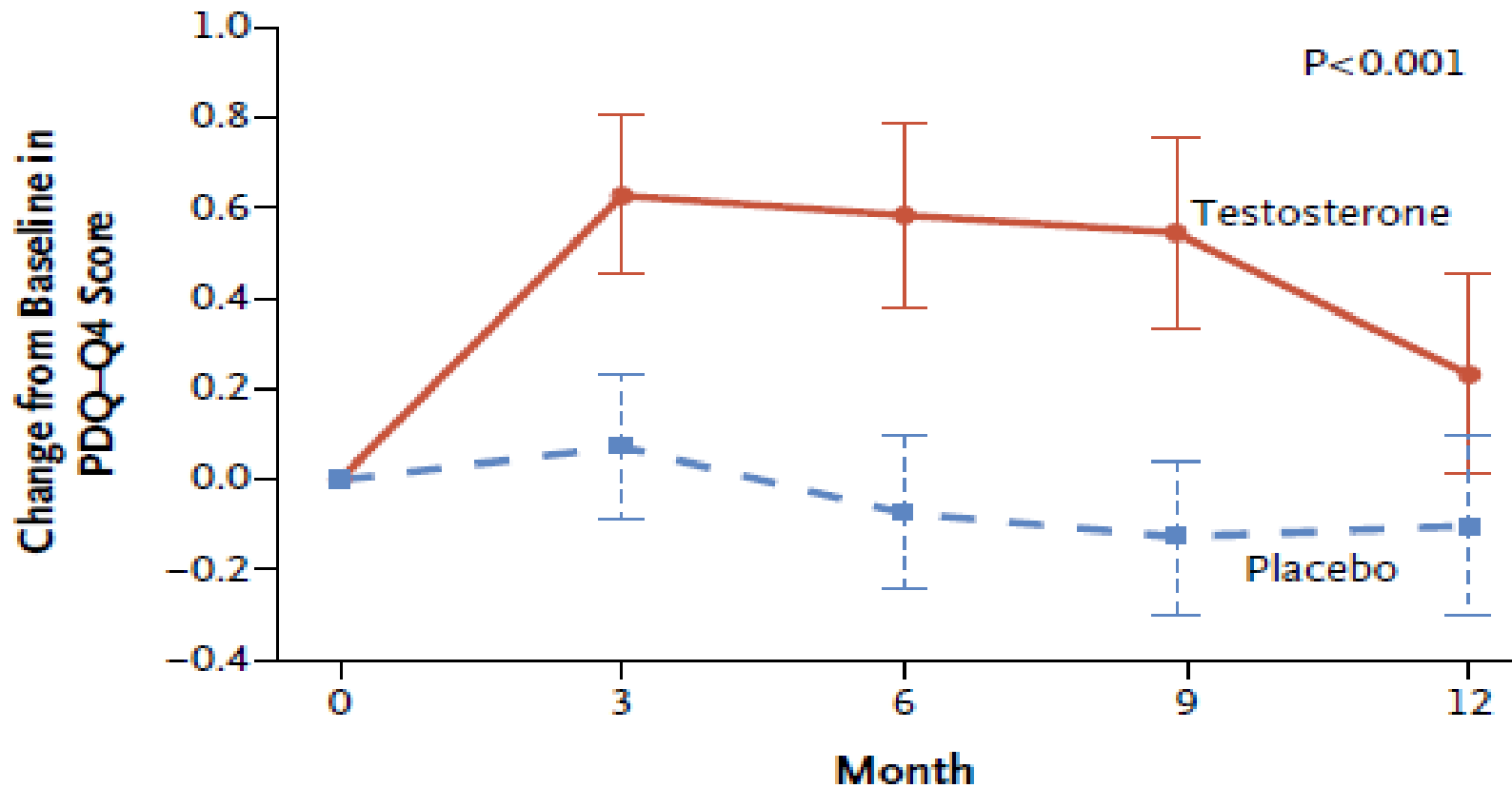
Placebo

No. at Risk					
Testosterone	230	205	208	205	193
Placebo	229	198	189	190	193

Benefits of walking ability

B **Walking Ability**
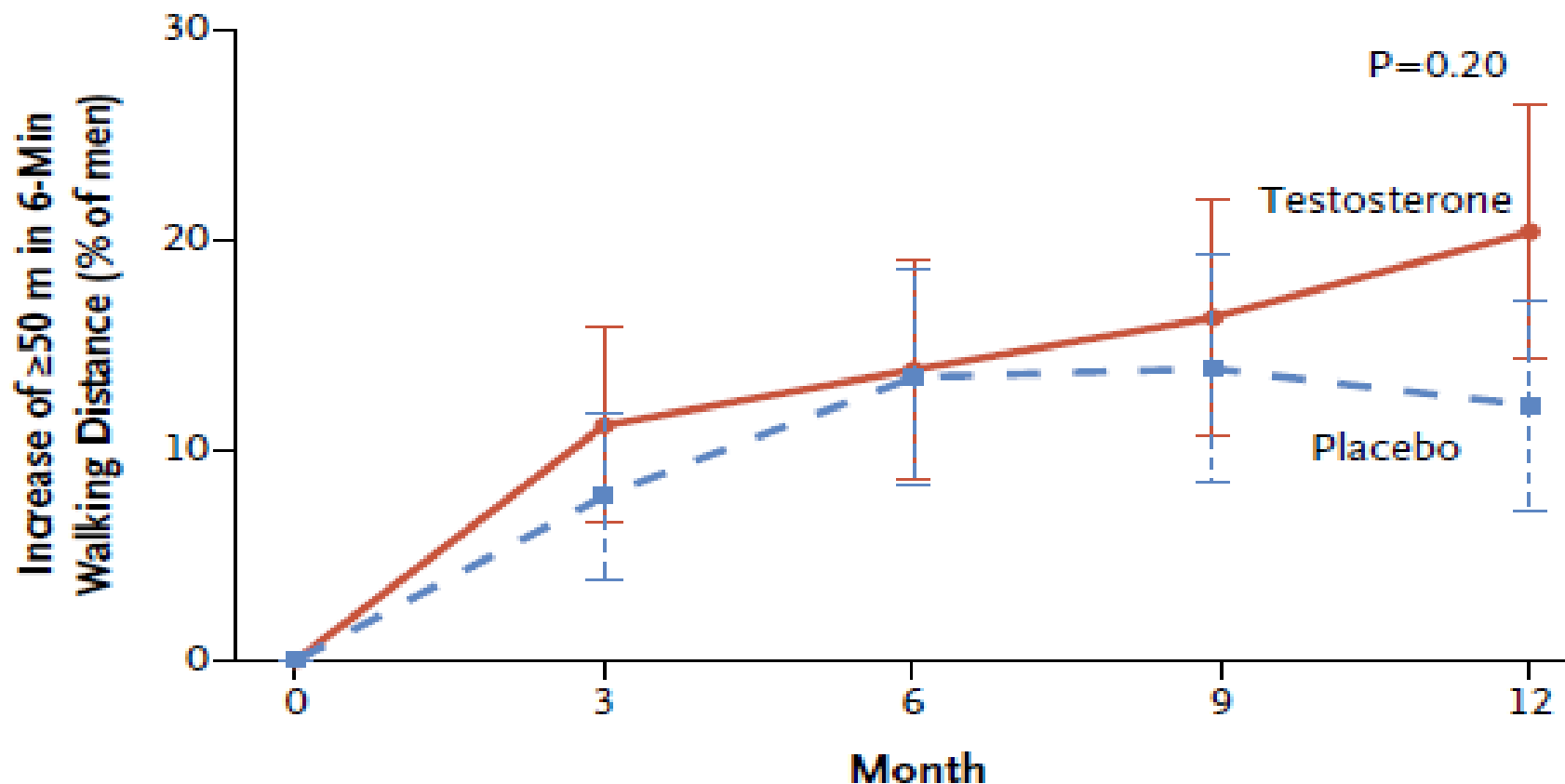
Benefits on vitality score

C Vitality
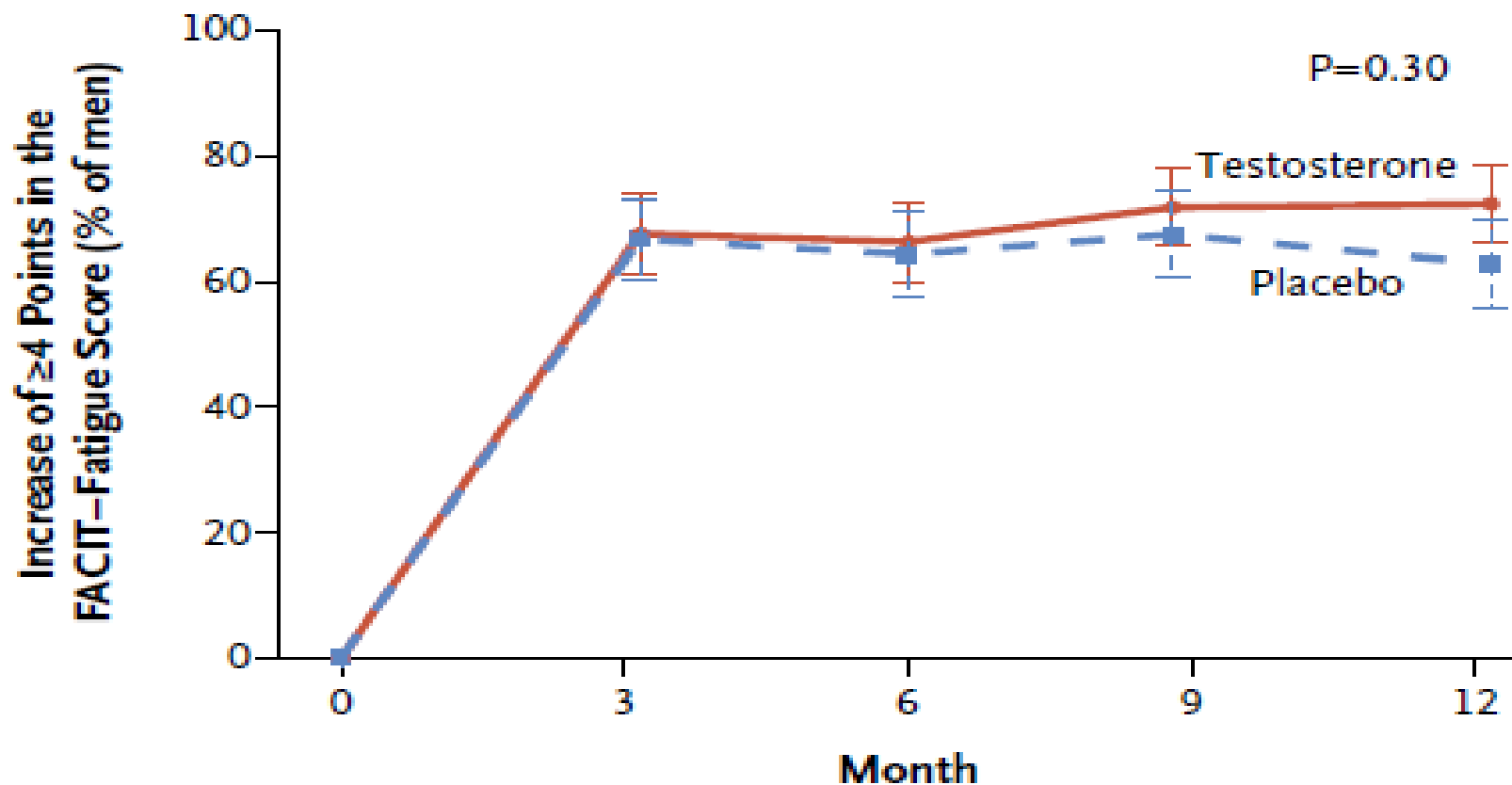
No. at Risk

Testosterone	236	219	217	206	203
Placebo	238	207	196	188	191

Table 4. Adverse Events during the First Year (Treatment Period) of the Testosterone Trials.*

Event	Placebo (N = 394)	Testosterone (N = 394)
	no. of participants	
Prostate-related event		
Increase in PSA level by ≥1.0 ng/ml	8	23
Prostate cancer	0	1
IPSS >19†	26	27
Hemoglobin ≥17.5 g/dl	0	7
Cardiovascular event‡		
Myocardial infarction (definite or probable)	1	2
Stroke (definite or probable)	5	5
Death from cardiovascular causes	1	0
Myocardial infarction, stroke, or death from cardiovascular causes	7	7
Serious adverse events		
Death	7	3
Hospitalization	78	68
Other§	6	7

British Society for Sexual Medicine (BSSM) observations

- Testosterone therapy for men with testosterone deficiency is effective, rational and evidence based

- There is no scientific basis for withholding testosterone therapy from men on the basis of age

British Society for Sexual Medicine (BSSM) observations

- Increased CVD risk with testosterone is unsupported by the studies

- Deficiency is associated with increased CVD and mortality

  Increase d risk of prostate cancer is also unsupported

- A major research initiative to explore the benefits of testosterone therapy in cardiometabolic disease is overdue

Endocrine Society Recommendations

- a) low levels of testosterone (< 300 ng/dl)

- b) Symptoms of low testosterone

Challenges of Testosterone Replacement

- Clinical features of deficiency are nonspecific
- Marked variations in the reference range
- Concern on prostate and breast cancer, Cardiovascular outcome, thrombosis, sleep apnoea, mortality
- Choosing appropriate formulations
- Follow up

- Overcoming the challenges

Prerequisite Investigations are

- Complete blood count with ESR
- kidney function
- liver function
- Lipid profile
- PSA
- Serum testosterone level
- TFT

Not Recommended

- **<u>Prostate or breast cancer</u>**

- Nodule on the prostate on DRE
- PSA > 3 ng/ml
- Hematocrit > 50%
- Obstructive sleep apnea
- LUTS (Score>19)
- Class III or IV heart failure

Available Testosterone Preparations

Route of administration	Substance	Format	Suggested dose	Notes
Intramuscular injection	Testosterone undecanoate (Nebido)	1000-mg injection	1000 mg every 9–16 weeks	Concerns by FDA regarding risk of pulmonary oil microembolism and anaphylactic reactions
Intramuscular injection	Testosterone enanthate (Testoviron)	250-mg injection	250 mg every 2–4 weeks	Risk of symptomatic high/low serum values
Transdermal	Testosterone (Testim, Testogel, Tostran)	Gel	50 mg d^{-1}	Risk of incidental transfer to others, avoid skin contact with women and children
Transdermal	Testosterone (Androderm) (Testoderm)	Skin patch / Scrotal patch	5–15 mg d^{-1} / 2.5–10 mg d^{-1}	Patches may cause skin irritation
Subcutaneous	Testosterone (Implants)	Pellet	400–800 mg every 4–6 months	Requires surgical (minor) procedure. Risk of extrusion
Buccal	Testosterone (Striant)	Buccal adhesive	60 mg d^{-1}	Gum-related adverse effects. Risk of transfer with intimate contact (saliva)
Oral	Testosterone undecanoate (Andriol)	40-mg capsule	120–160 mg d^{-1}	Peak concentrations after 4 hours. Considerable individual variation in uptake

Common Testosterone Preparations

Formulation	Dose	Advantage	Disadvantage	Brand name
Testo. Enanthate	100-200 mg every 2-4 weeks	Inexpensive	Fluctuation of blood level	Fluctuation
Testo. Cypionate	100-200 mg every 2-4 weeks	Inexpensive	Fluctuation of blood level	Fluctuation
Scrotal patch	One 6mg patch/day	Less irritant	Scrotum shaving	Testoderm
Nonscrotal patch	5-10 mg/day	Ease of application	Erratic absorption	Testoderm TTS/Androderm
Buccal tab	30 mg bid	Effective	Mouth irritation	Striant

Common Testosterone Preparations

Formulation	Dose	Advantage	Disadvantage	Brand name
Long acting Testo undecanoid	1000mg> 1000 mg(6 week)> 10000 mg 3 monthly	Less frequent inj.	FDA approval not yet	Aveed/ Nebido
Mixture of Propionate 30 Phenylpropio 60 Isocaproate 60 Decanoate 100	250 mg every three weeks	Rapid rise of level	Local reaction Frequent Inj	Testanon Testonon
Oral Test Undecanoate Caps 40 mg	160 mg to 320 mg/day in divided doses	Easy administration	Erratic absorption ?Hepatic neoplasm Not FDA approved	Andriol Caps

Follow up of TRT

- Follow up at 3-4 months interval in first year with S. testosterone, PSA, LFT, CBC

- There after yearly

- Digital rectal examination at base line and periodically

Conclusions

- **Andropause as male counterpart of menopause is nonexistent**
- **Age-related decline in androgen is noted in 20-40% males beyond 40 years**
- **TRT is strongly recommended for symptomatic males**
- **Contraindications/cautions about Prostatatic , Cardiac and hematological diseases are to be considered**
- **Choosing appropriate preparations should be individualized**
- **More researches will hopefully illuminate this area in near future**

Acknowlededements

- ## Prof. Khan Abul Kalam Azad
- Principal and Head of the Dept. of Medicine, DMC
- ## Dr. Indrajit Prasad
- Assoc. Prof. of Endocrinology, DMC
- ## Dr. Moinul Islam
- Registrar, Endocrinology, DMC
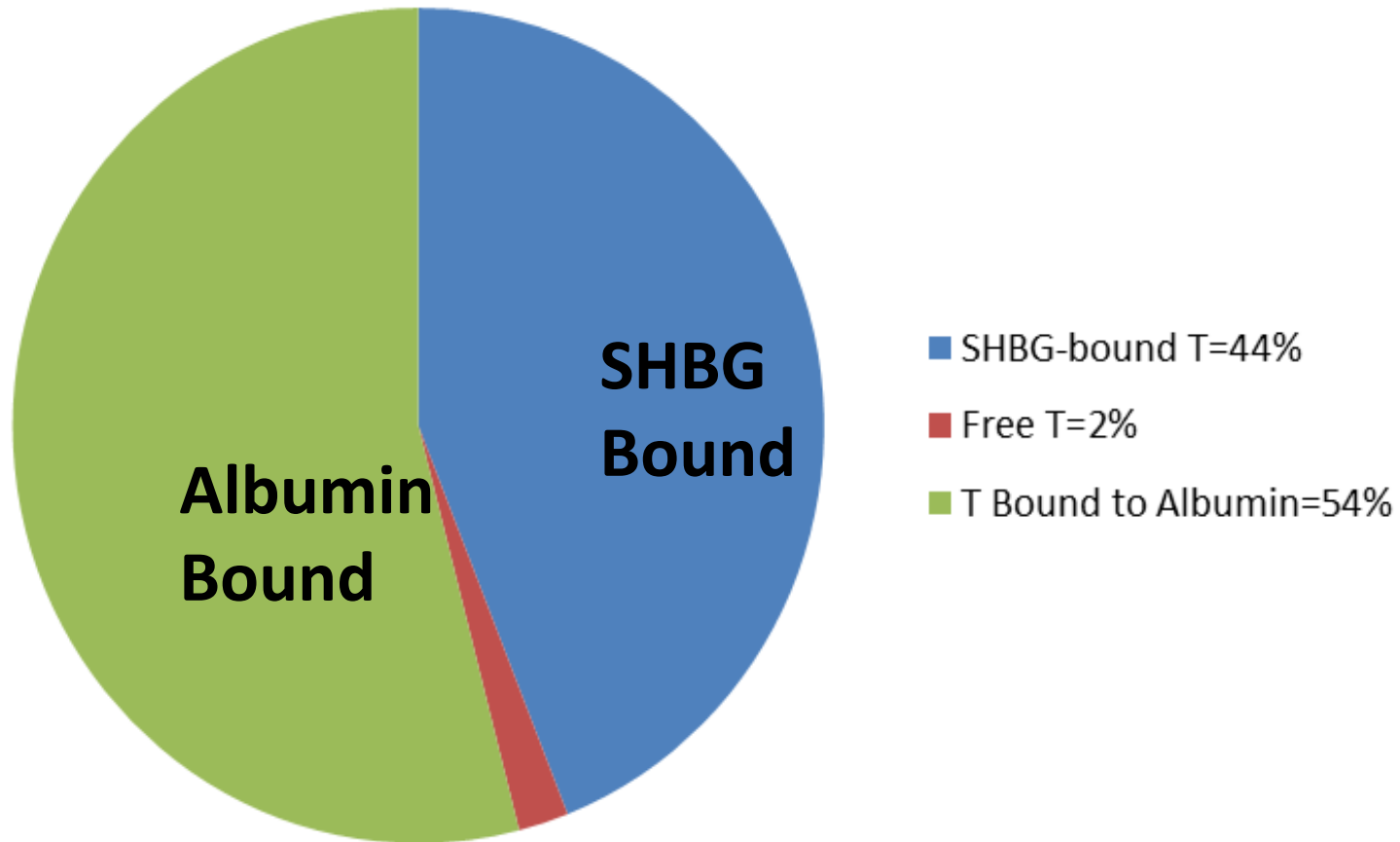- ## Dr. Mostofa Kamal Chowdhury
- Asst. Registrar, Endocrinology, DMC

THANK YOU

Total testosterone ref (ng/dl)

Age	Total Testosterone
19-24	700
25-34	658
35-44	617
45-54	606
55-64	562
65-74	524
75-84	471
85-100	376

Total Testosterone Reference Range by Age

Testosterone Fractions

■ SHBG-bound T=44%

■ Free T=2%

■ T Bound to Albumin=54%

Gonadal Hormones & Gonadotrophins in healthy males beyond forty years
Ansari MA J et al. JPMA:56:203;2006