Male Hypogonadism and Testosterone therapy

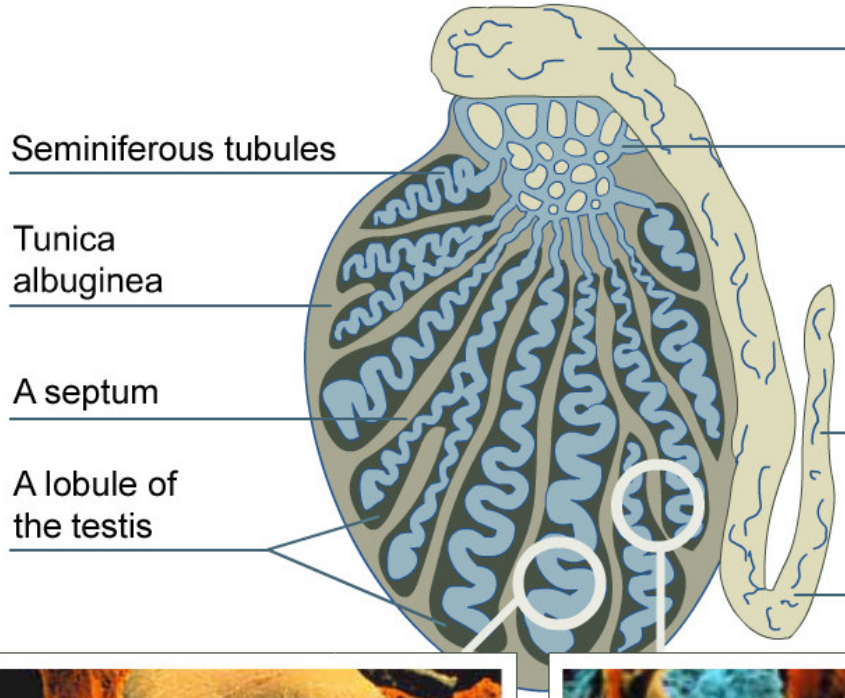
Ketan Dhatariya

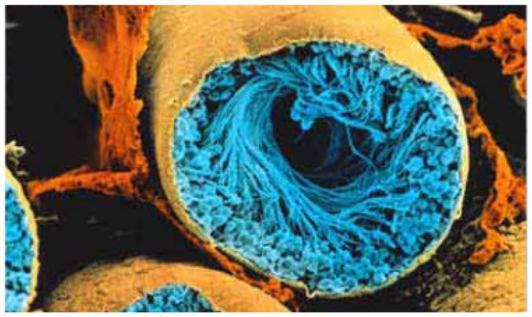
Overview: Male Hypogonadism

- Physiology of testosterone secretion
- Aetiology and clinical features
- Epidemiology
- Diagnosis
- Indications for treatment
- Treatment options
- Monitoring
- Conclusion

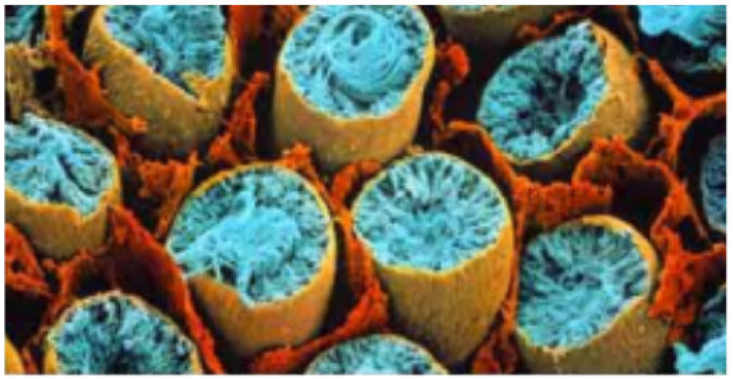
Physiology of testosterone secretion

Testis structure



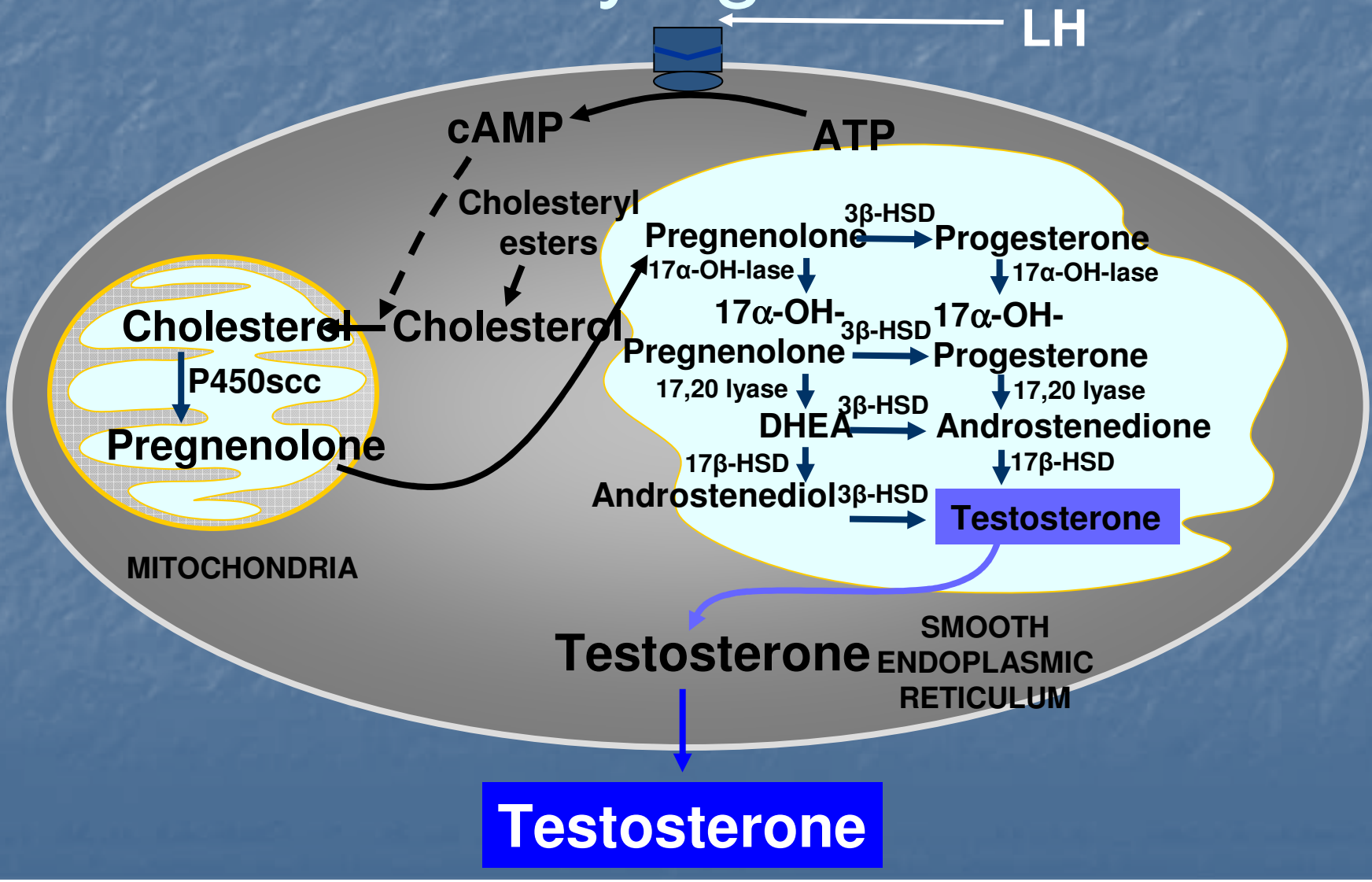


Seminiferous tubules with germinal epithelium (blue)

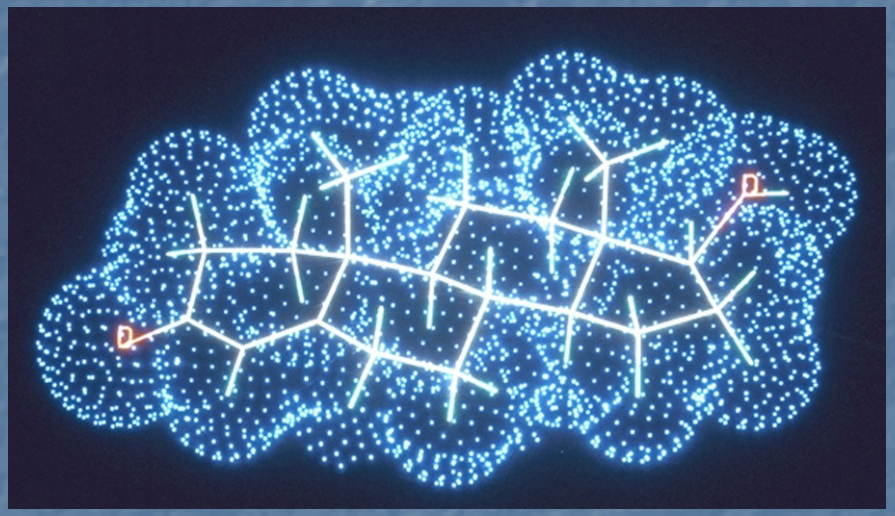


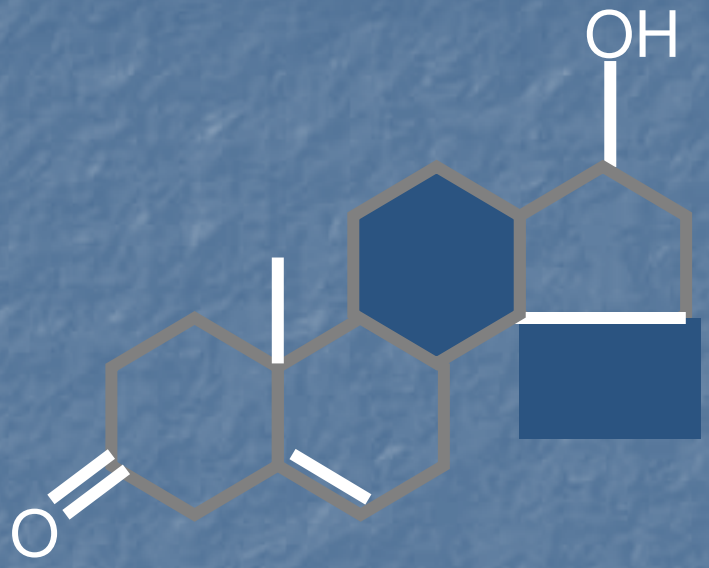
Between the seminiferous tubules lie the testosterone-producing Leydig cells (orange)

Testosterone synthesis in the Leydig cell



Testosterone

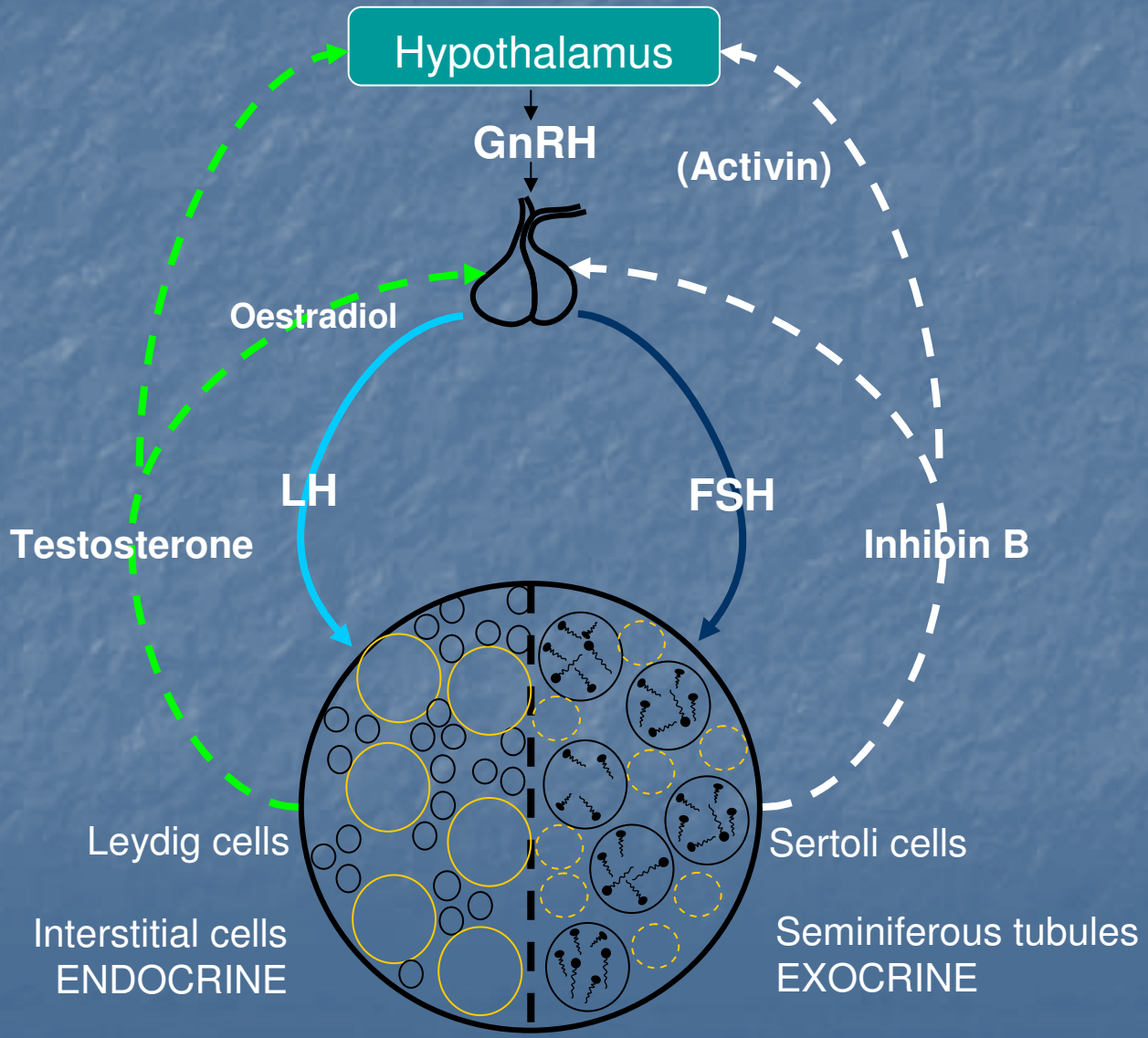




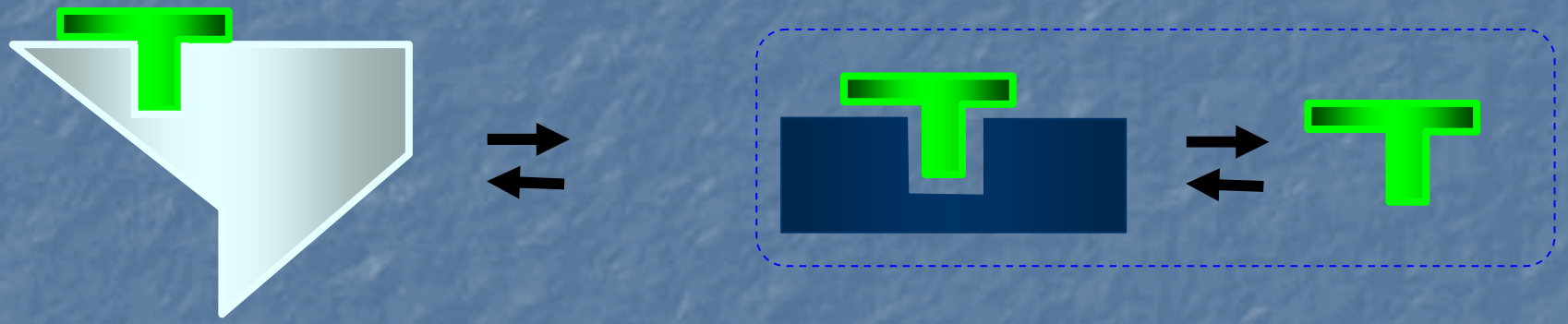
- Testosterone is the most important hormone produced by the testis
  - Between 5 and 7mg of testosterone are produced by the Leydig cells daily in adult men

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

Regulation of Testicular Function



Binding of Testosterone



T firmly bound to SHBG

60%

T loosely bound to albumin

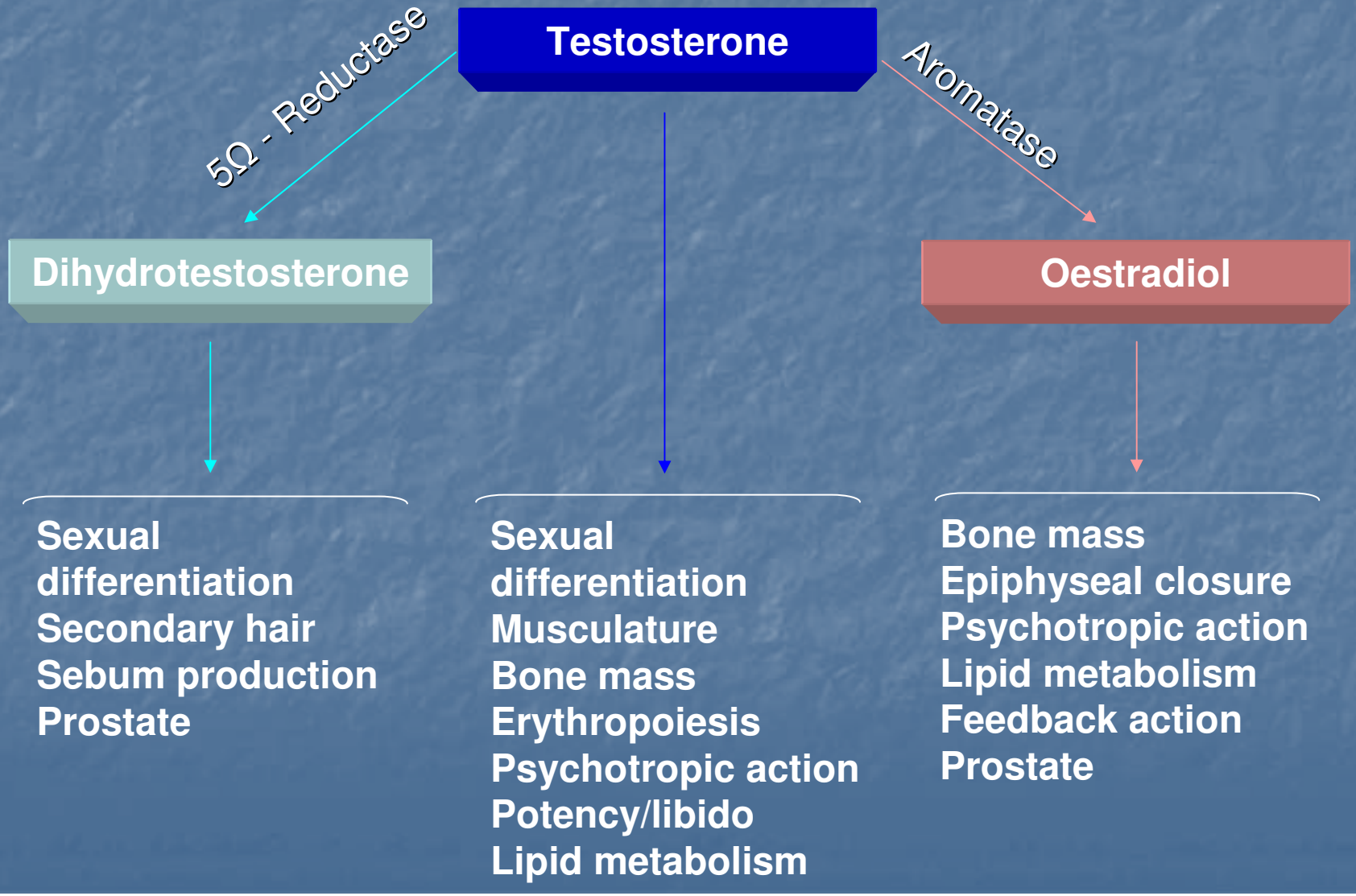
38%

Free T

2%

BIOAVAILABLE TESTOSTERONE
= Albumin-bound T + Free T

Testosterone and its Metabolites



Hypogonadism: Aetiology and Clinical Features

Hypogonadism

- Hypogonadism is inadequate function of the testes
- Prevalence: 5 men in 1000 in the UK
  - 2-4 million men in the US, estimated only 5% treated
- Diagnosis: clinical symptoms and biochemical tests
- Presentation
  - Pre-pubertal: lack of secondary sexual development in teens
  - Post-pubertal: insidious onset, features overlapping with many systemic conditions, infertility

Petak SM et al. *Endocrine Pract* 2002;8:439-456. Nieschlag E et al. *Eur Urol* 2005;48:1-4. Handelsman DJ. *Androgens*. In: Male reproductive endocrinology; Ed. Mclachlan RI. Endotext.com; 2002 Rhoden EL & Morgentaler A. *NEJM* 2004;350:482-92.

Clinical Picture of Testosterone Deficiency

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

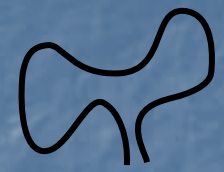
- Osteoporosis
- Raised lipids
- Insulin resistance
- Sarcopaenia

Reproductive system

- Subfertility
- Subnormal genital size
- Loss of pubic hair
- Erectile dysfunction
- Sexual dysfunction

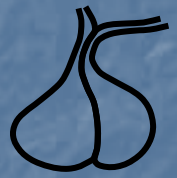
Nieschlag E and Behre HM. Testosterone: action, deficiency, substitution (3rd Edition). Cambridge University Press; 2004.

Sex Hormones and Hypogonadism



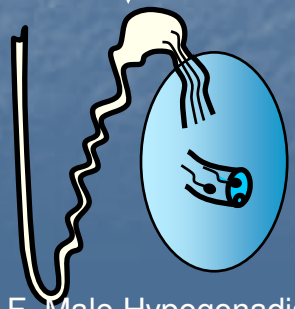
Hypothalamus

GnRH



Pituitary

FSH LH



Testis

SECONDARY HYPOGONADISM

Secondary testicular failure

Hypogonadotrophic hypogonadism

PRIMARY HYPOGONADISM

Primary testicular failure

Hypergonadotrophic hypogonadism

Jöckenhovel F. Male Hypogonadism. UNI-MED, Bremen; 2004.

Causes of Primary Hypogonadism

- Congenital
  - Chromosomal defects e.g. Klinefelter's syndrome
  - Congenital anorchia
  - Androgen receptor/enzyme defects
- Acquired
  - Testicular trauma/torsion
  - Surgical removal
  - Chemotherapy/irradiation
- Complications of illness
  - e.g. diabetes, renal failure, alcoholic liver disease, cirrhosis

Nieschlag E et al. *Human Reprod Update* 2004;10(5):409-419.

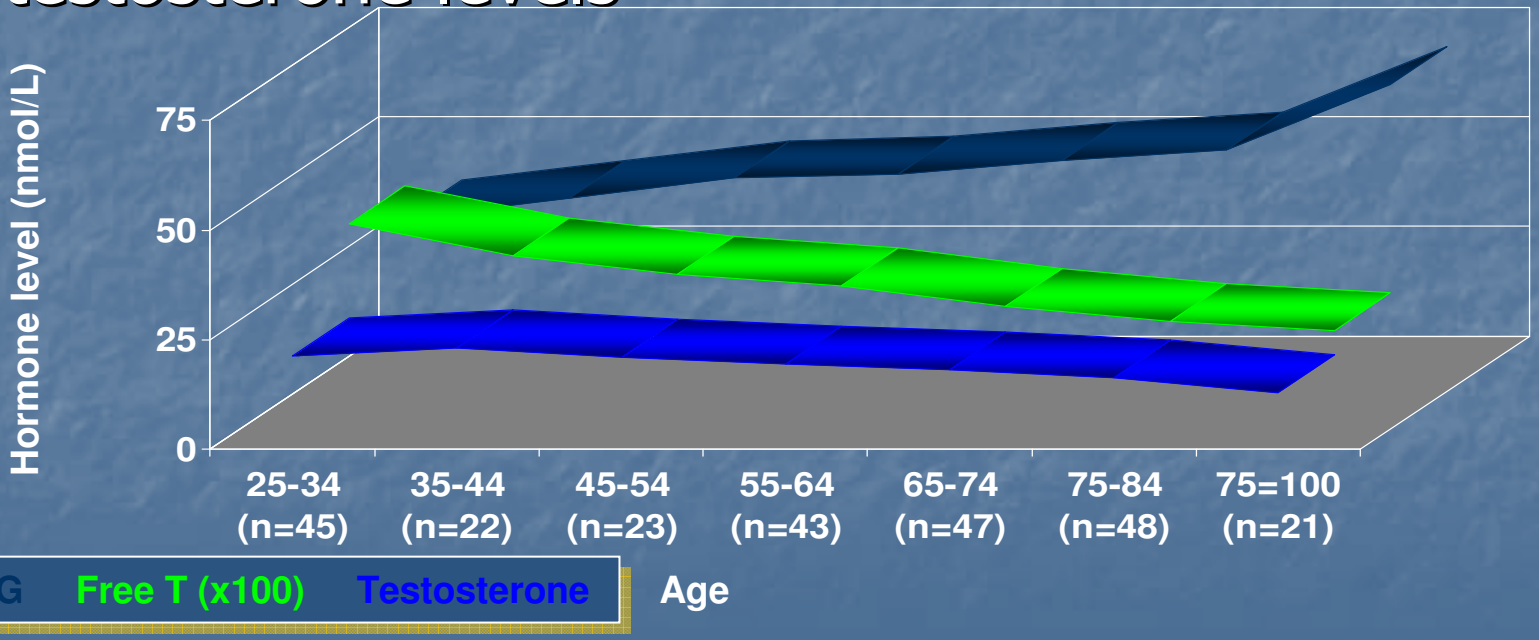
Causes of Secondary Hypogonadism

- Congenital
  - Kallmann's syndrome
  - Idiopathic hypogonadotrophic hypogonadism (IHH)
  - Prader-Willi syndrome
- Acquired
  - Prolactinoma
  - Pituitary adenoma
  - Hypothalamic tumour
  - Anabolic steroid abuse
- Complications of illness
  - e.g. AIDS, haemochromatosis

Nieschlag E & Behre HM. Andrology, Male reproductive health and dysfunction (2nd Edition). Springer, Heidelberg; 2002.
Nieschlag E et al. *Human Reproduct Update* 2004;10(5):409-419.

Late-onset Hypogonadism

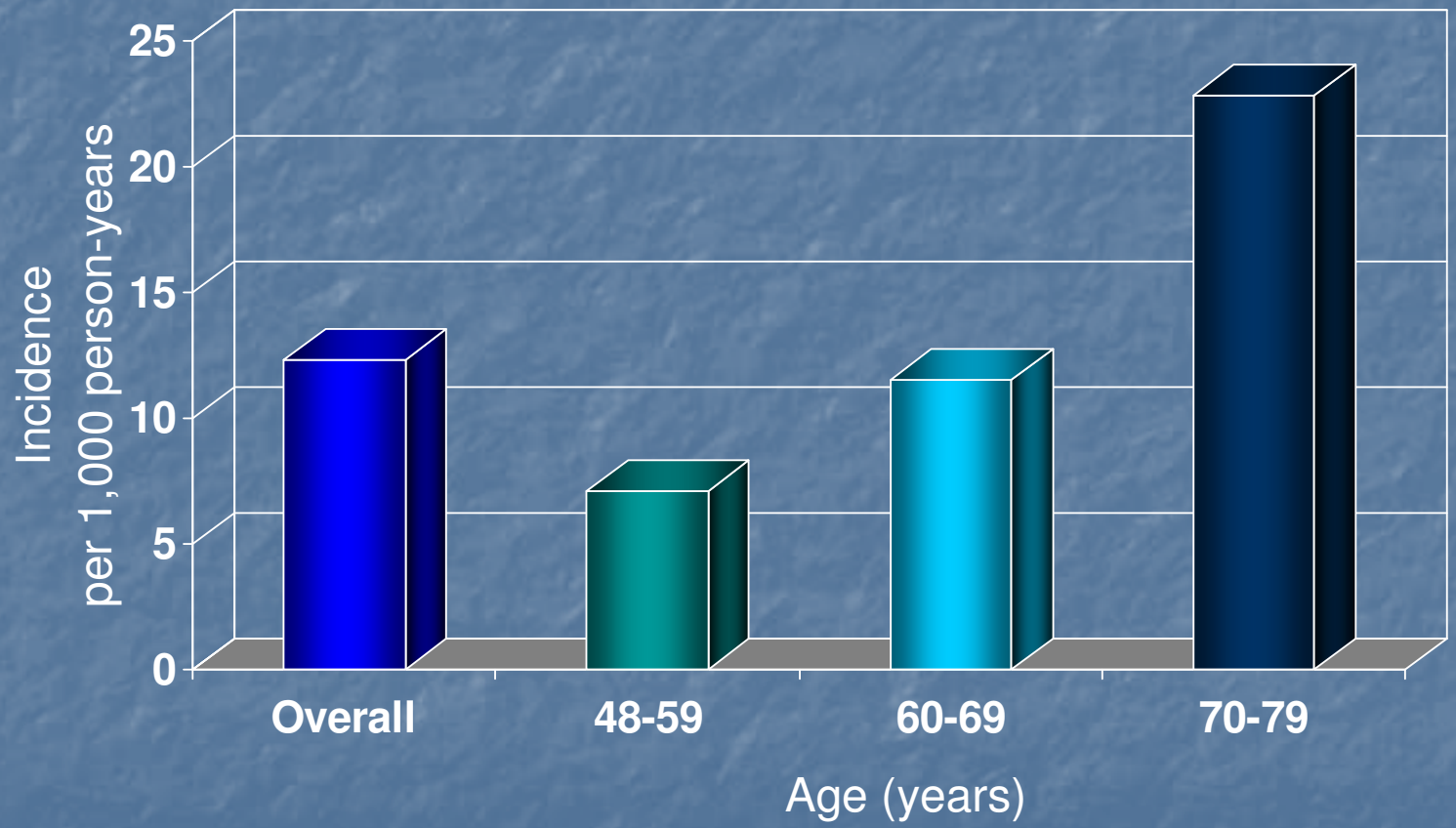
- A clinical and biochemical syndrome associated with advancing age and characterised by typical symptoms and a deficiency in serum testosterone levels



Nieschlag E et al. *Eur Urology* 2005;48:1-4.
Vermeulen A et al. *J Clin Endocrinol Metab* 1996;81:1821-1826.

Epidemiology

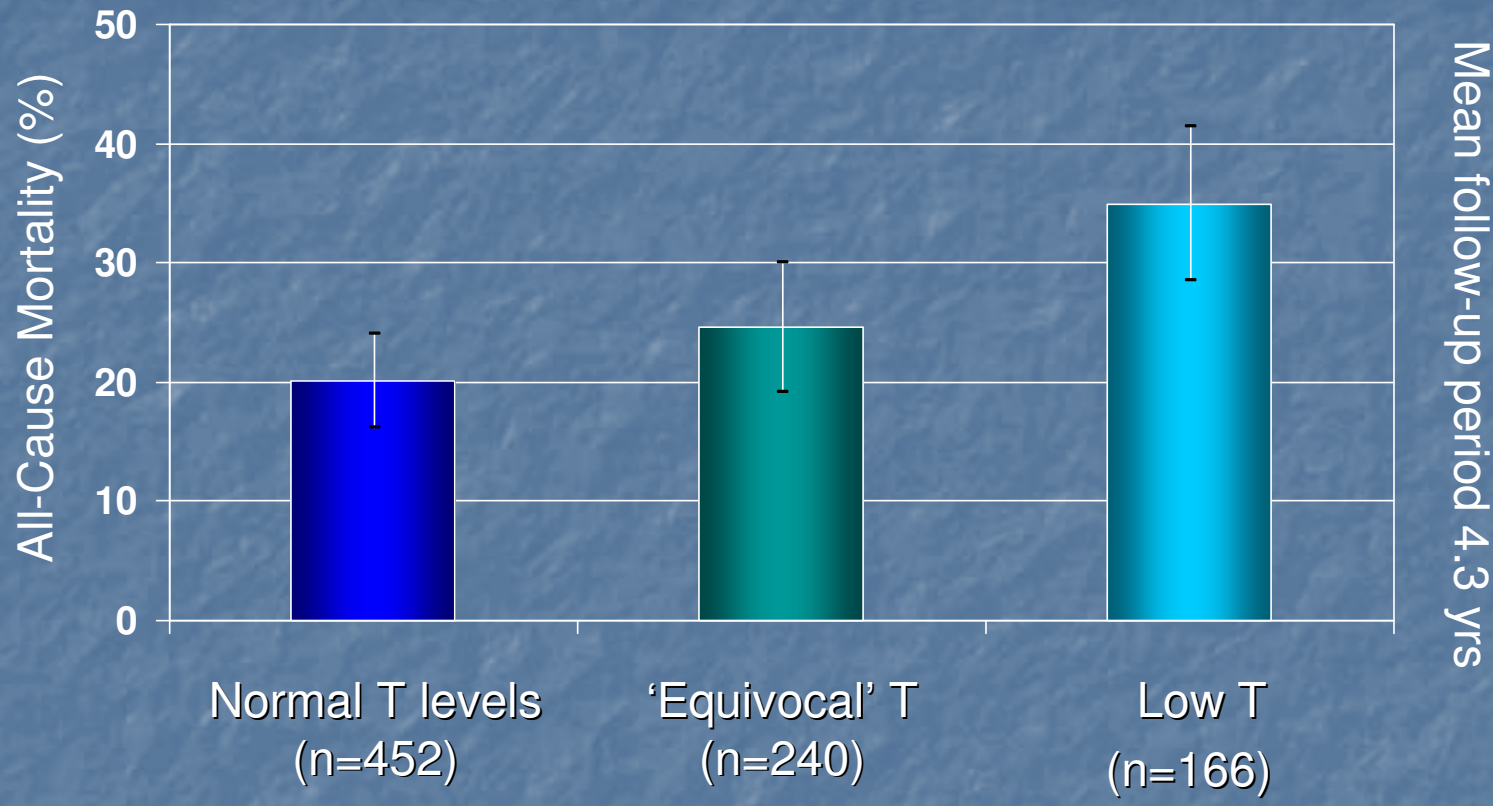
Hypogonadism Incidence and Age (US data)



- Expected 481,000 new cases p.a. in US men 40-69 yrs

Araujo A et al. *J Clin Endocrinol Metab* 2004;89(12):5920-5926.

Low Testosterone and Mortality



Hazard Ratio (adjusted)	1.00	1.38 (0.99-1.92)	1.88 (1.34-2.63)
Increased mortality risk	-	38% (*P* = 0.06)	88% (*P*<0.001)

Shores M et al. *Arch Intern Med* 2006;166:1660-1665

Hypogonadism and CV risk factors

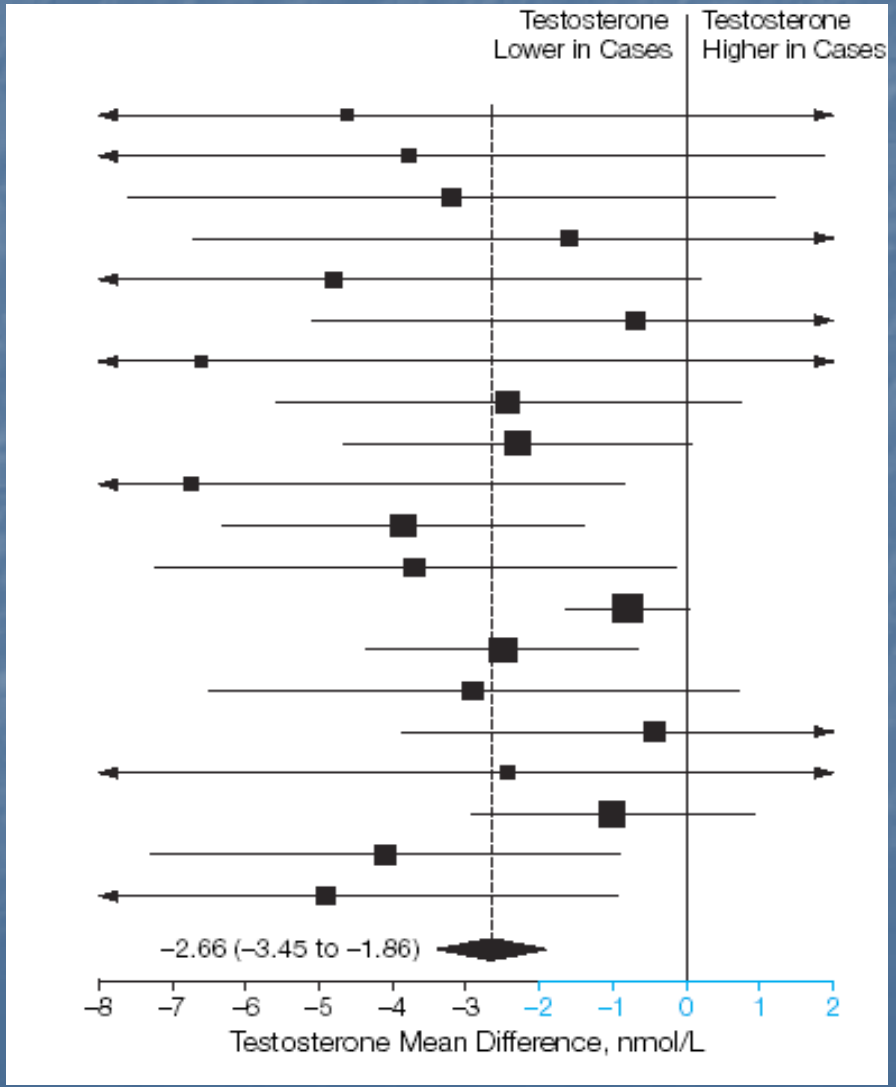
- Low testosterone levels in men frequently co-exist with
  - Type 2 diabetes mellitus
  - Erectile dysfunction
  - Abdominal obesity
  - Other CV risk factors
- Component of the metabolic syndrome?

CV, cardiovascular

Testosterone levels in type 2 diabetes[1]

20 studies (total n=3825 men with diabetes)[1]

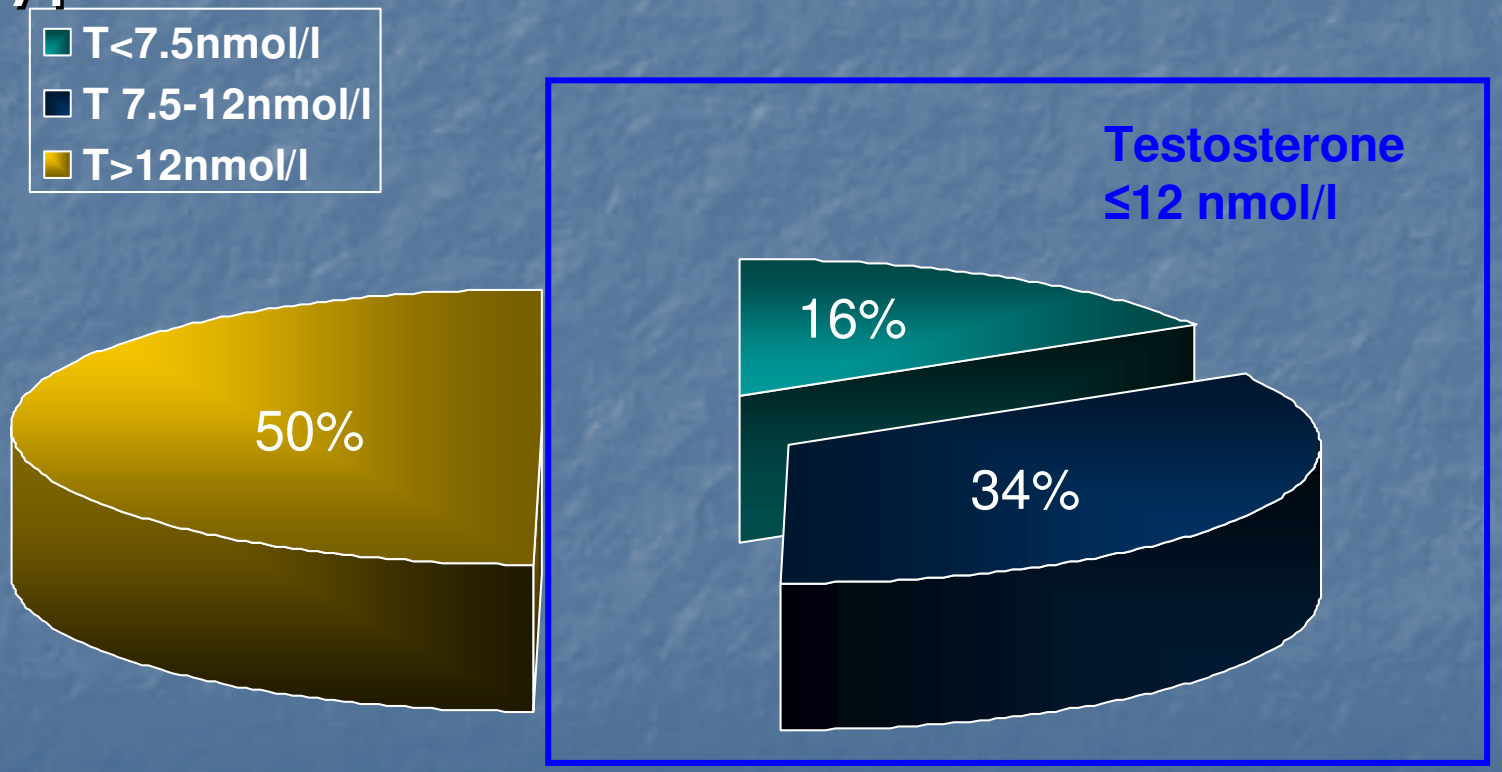
Calculated mean difference: -2.66 nmol/l (95% CI, -3.45 to -1.86)



1. Ding E et al. *JAMA* 2006;295:1288-1299.

Testosterone levels in type 2 diabetes[1]

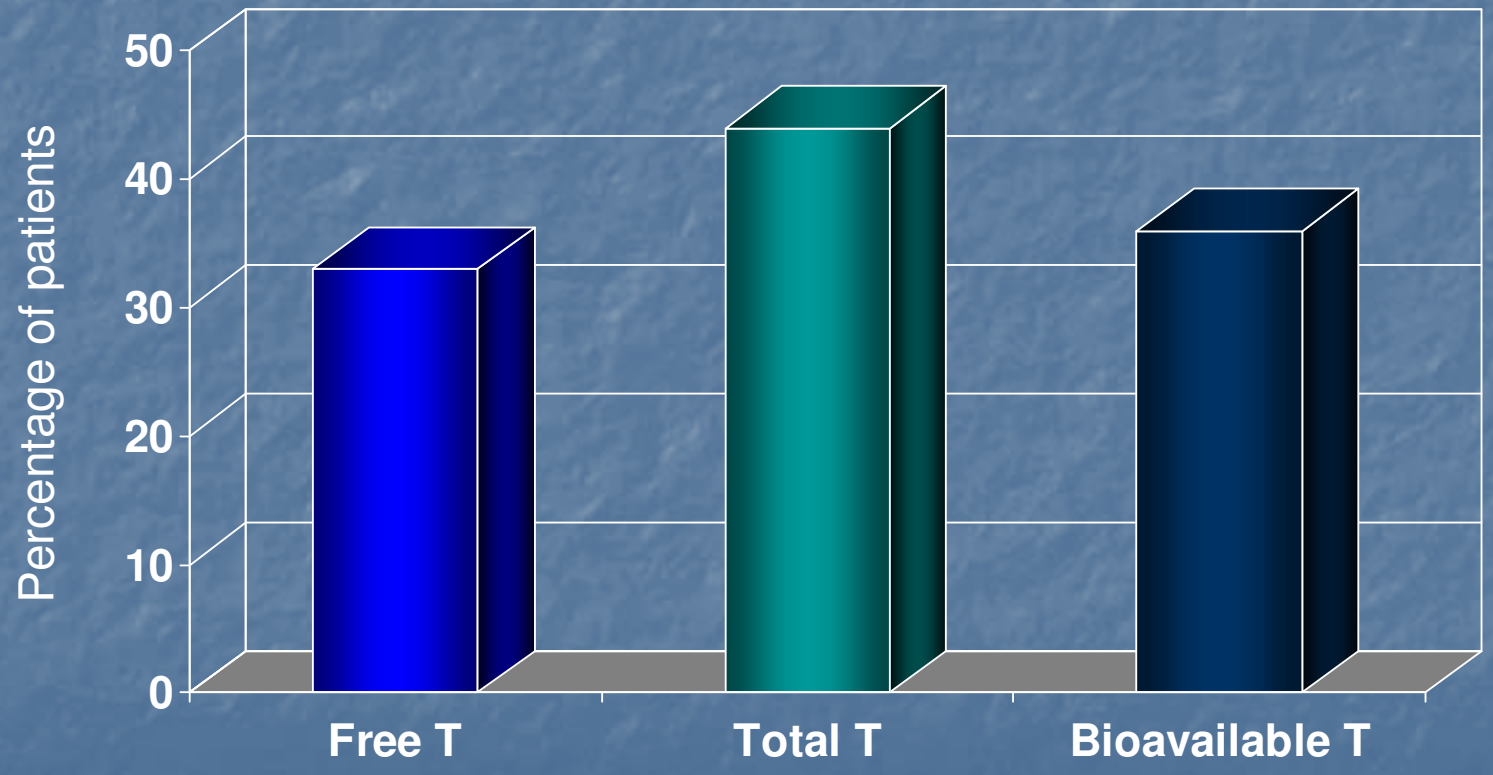
- 300 UK men (mean age, 58 yrs) with type 2 diabetes



1. Kapoor D et al. Endocrine Soc Abstract Book 2004: 448.

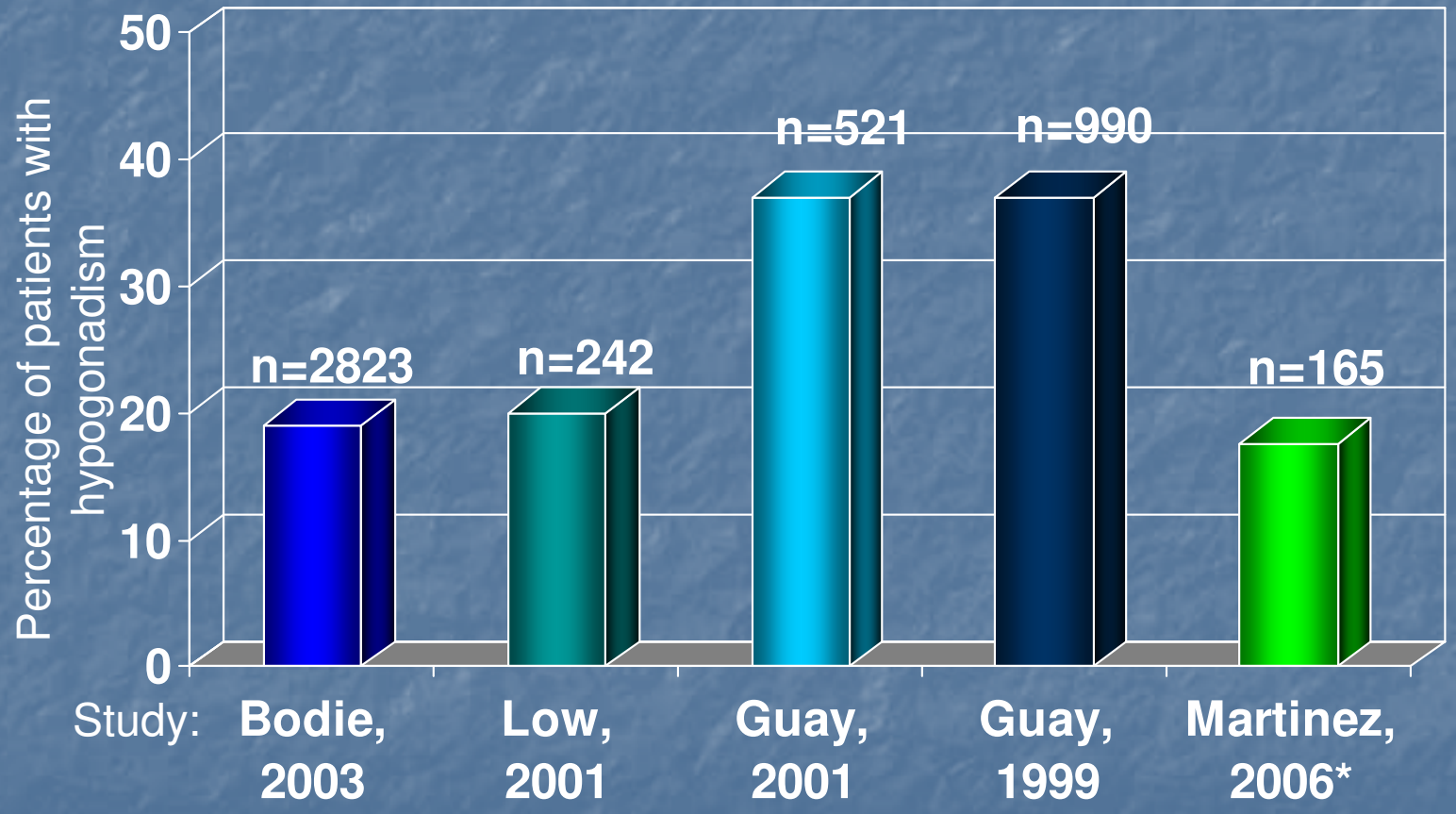
Prevalence of hypogonadism in diabetes

- n=103 men with type 2 diabetes



1. Dhindsa S et al. *J Clin Endocrinol Metab* 2004; 89(11): 5462-5468.

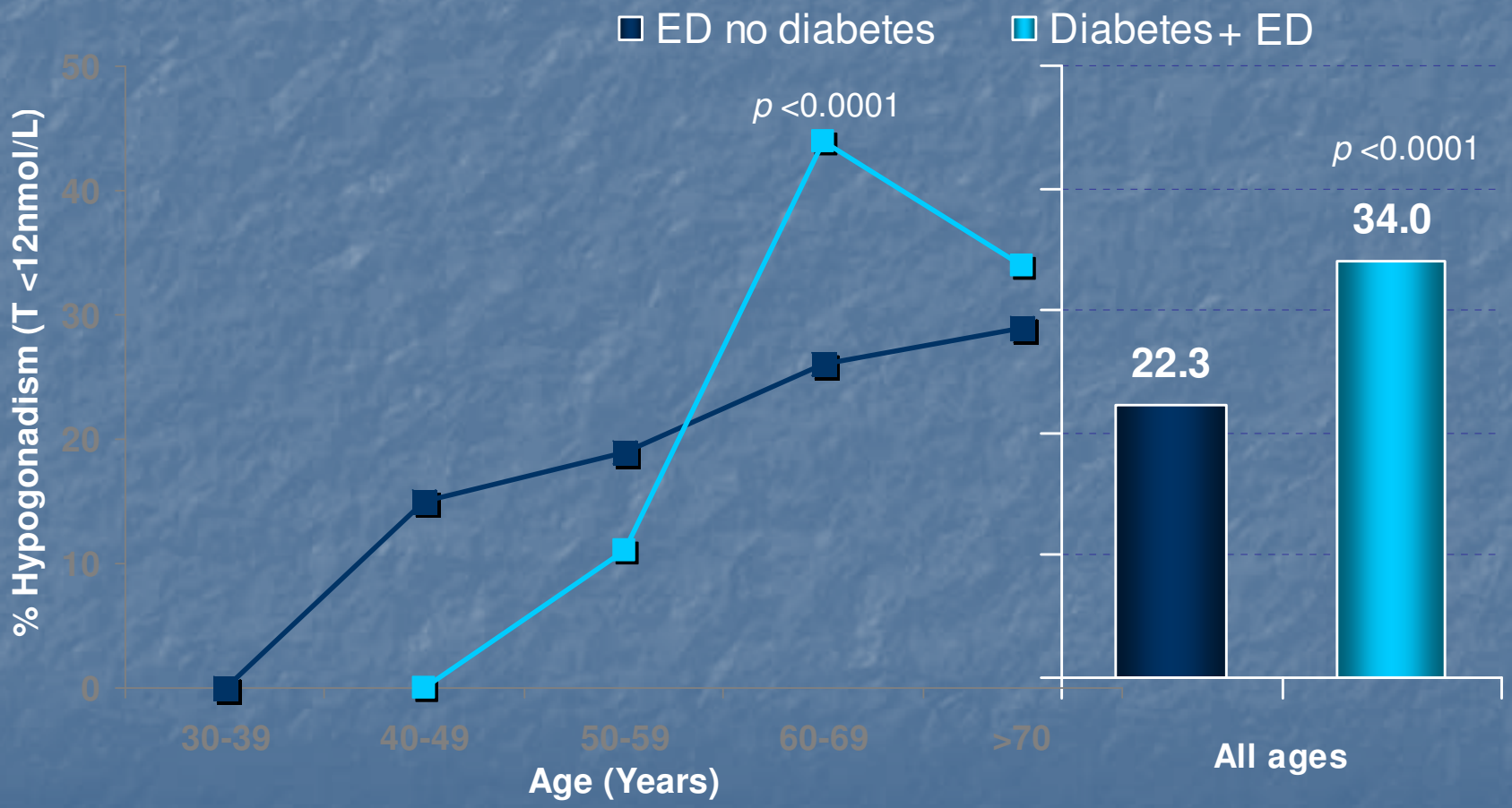
Prevalence of hypogonadism in ED



1. Bodie J et al. *J Urol* 2003; 169:2262-2264.
2. Low WY et al. *J Sex Med* 2004;1, Suppl. 1:111.
3. Guay AT et al. *J Androl* 2001;22(5):793-797.
4. Guay AT et al. *Endocr Pract* 1999;5(6): 314-321.
5. Martinez-Jabaloyas JM et al. *BJU Int* 2006;97:1278-1283.

*Diagnosed from free testosterone level

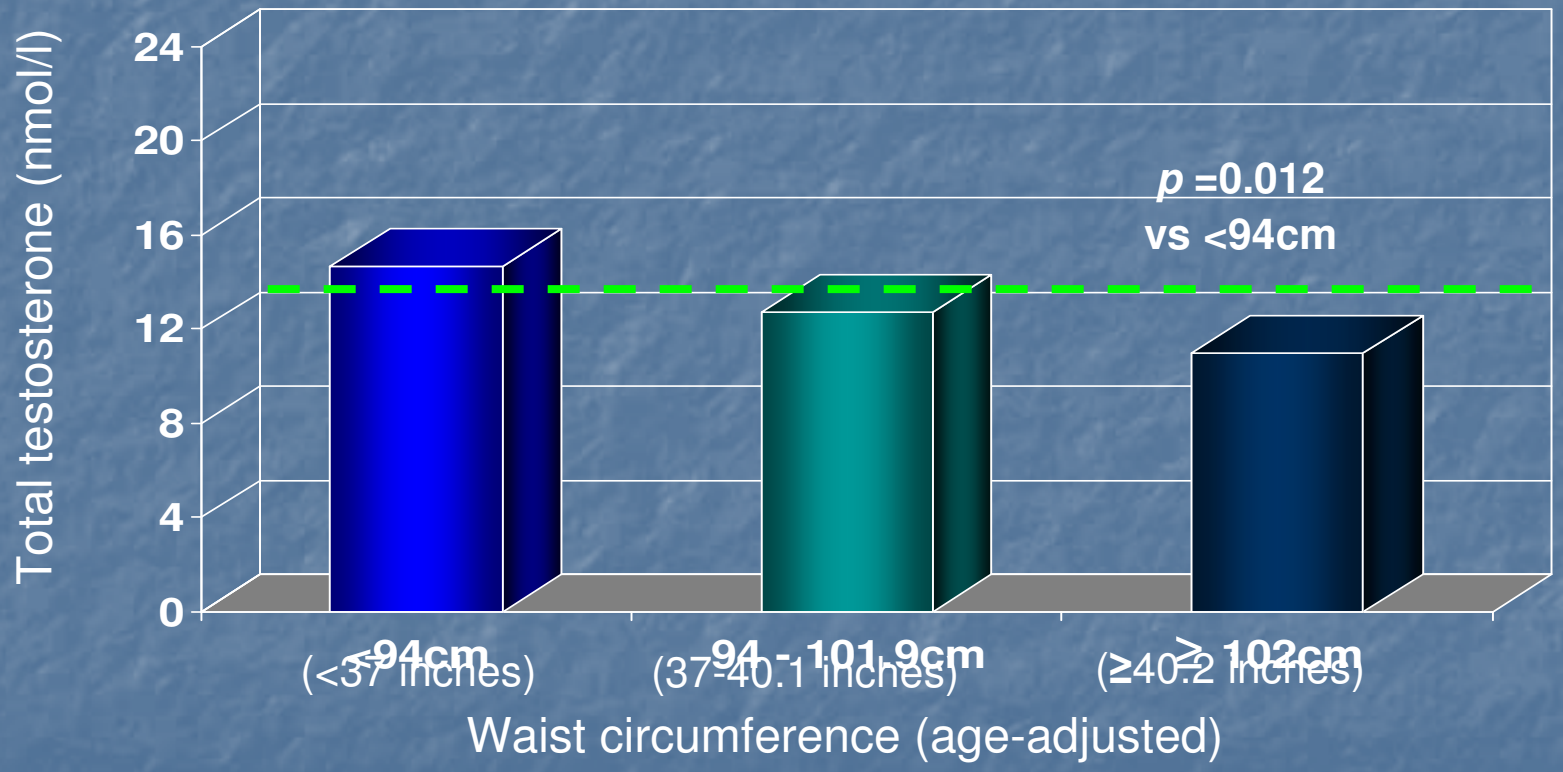
Hypogonadism in diabetic vs nondiabetic men with ED[1]



n=1027 men with ED with and without type 2 diabetes mellitus

1. Corona G et al. *Eur Urol* 2004; 46(2): 222-228.

Waist circumference and testosterone level[1]

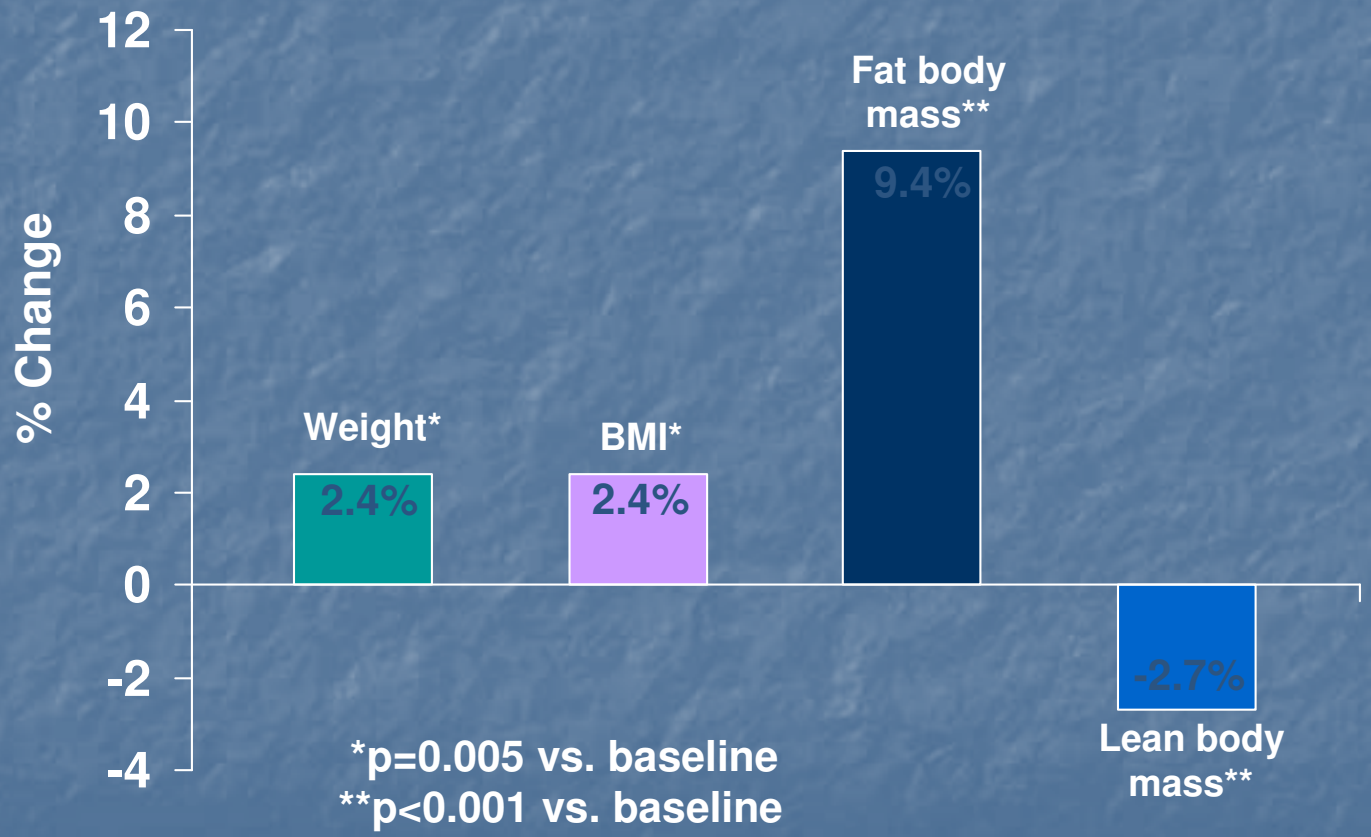


- The Tromsø Study: n=1548 community-dwelling men (age 25 – 84)[1]

1. Svartberg J et al. *Europ J Epidemiol* 2004;19:657-663.

Changes in body composition associated with androgen deprivation[1]

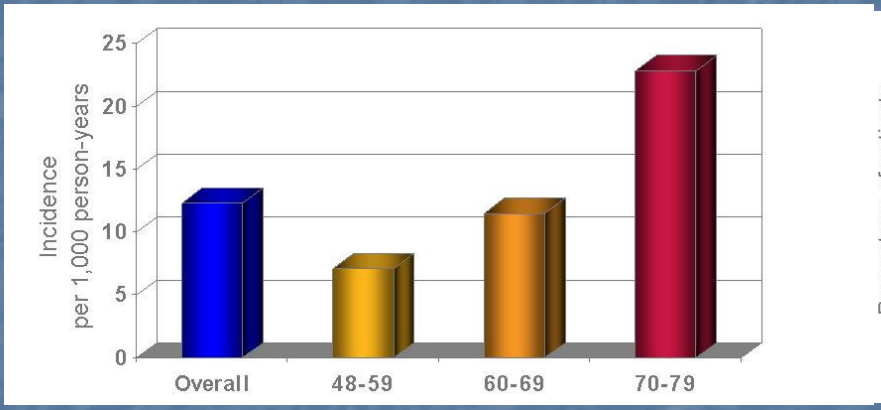
n=32 men with non metastatic prostate cancer, treated with leuprolide for 48 weeks. Serum testosterone levels fell by 96%.



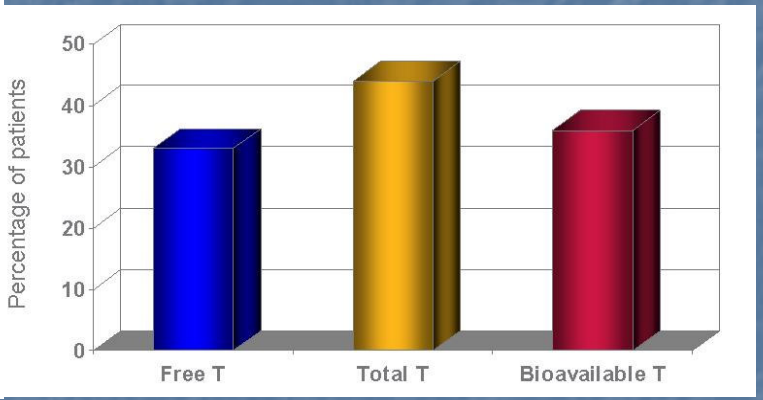
1. Smith MR et al. *JCEM* 2002;87:599-603.

Hypogonadism and CV risk factors

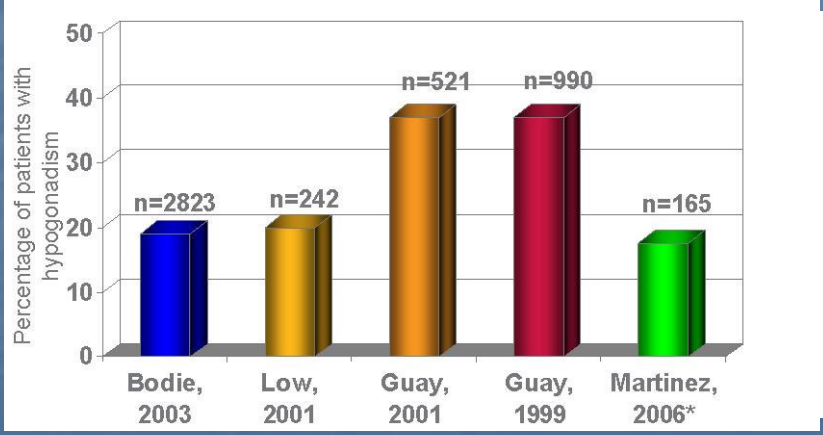
1. Hypogonadism and Age[1]



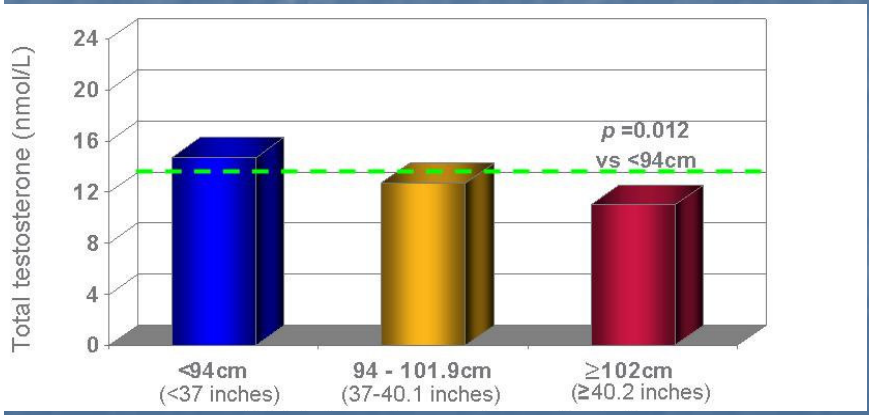
2. Hypogonadism and Diabetes[2]



3. Hypogonadism and ED[3-7]



4. Low T and WaistCircumference[8]



1. Araujo A et al. *J Clin Endocrinol Metab* 2004;89(12):5920-5926. **2**. Dhindsa S et al. *J Clin Endocrinol Metab* 2004; 89(11): 5462-5468. **3**. Bodie J et al. *J Urol* 2003; 169:2262-2264. **4**. Low WY et al. *J Sex Med* 2004;1, Suppl. 1:111. **5**. Guay AT et al. *J Androl* 2001;22(5):793-797. **6**. Guay AT et al. *Endocr Pract* 1999;5(6): 314-321. **7**. Martinez-Jabaloyas JM et al. *BJU Int* 2006;97:1278-1283. **8**. Svartberg J et al. *Europ J Epidemiol* 2004;19:657-

Diagnosing hypogonadism

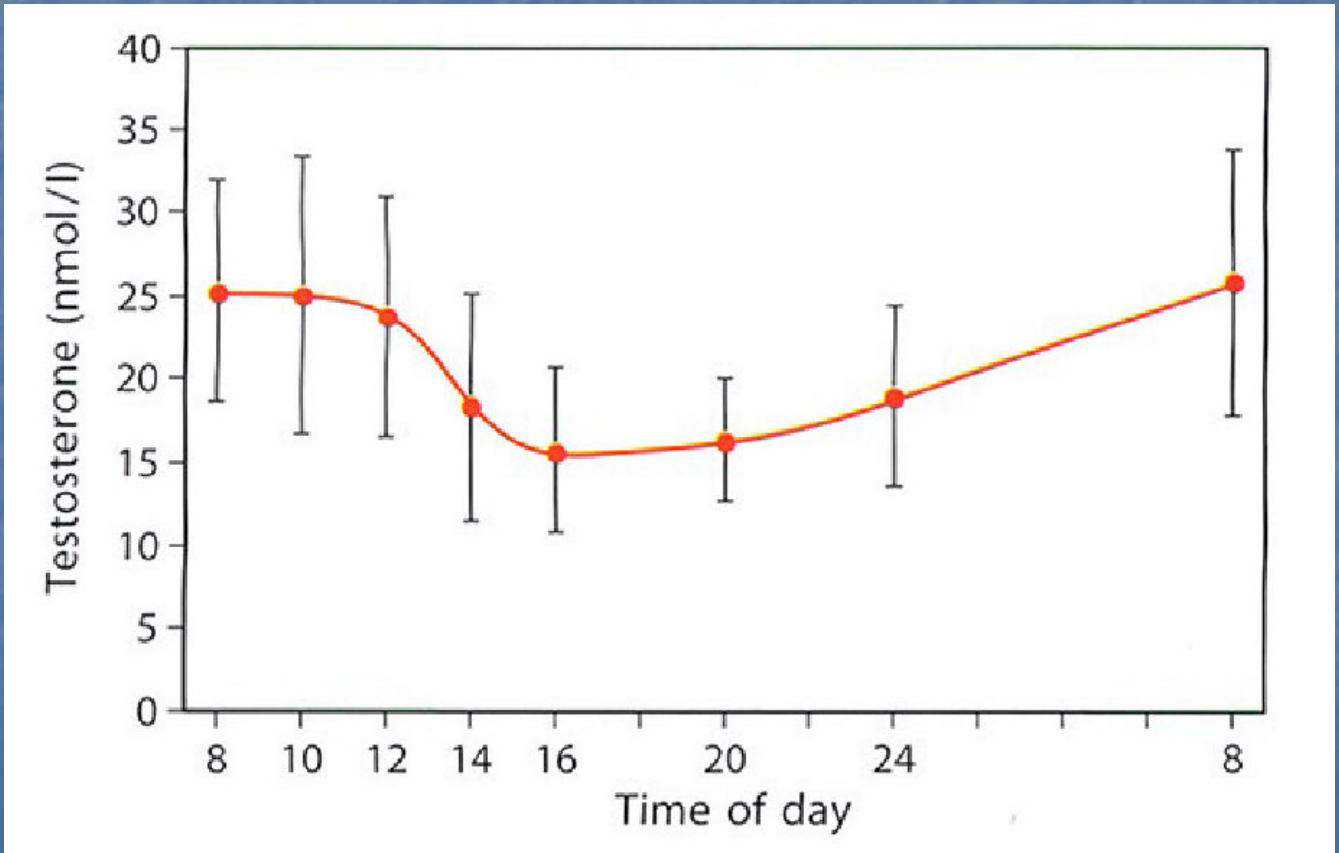
Diagnosis of hypogonadism[1]

- Appropriate assessment of symptoms as suggested by patient's history and physical examination
- Biochemical tests:
  - Total testosterone assay
  - Gonadotrophins: LH/FSH
  - Prolactin
  - SHBG (can be used to calculate free testosterone)

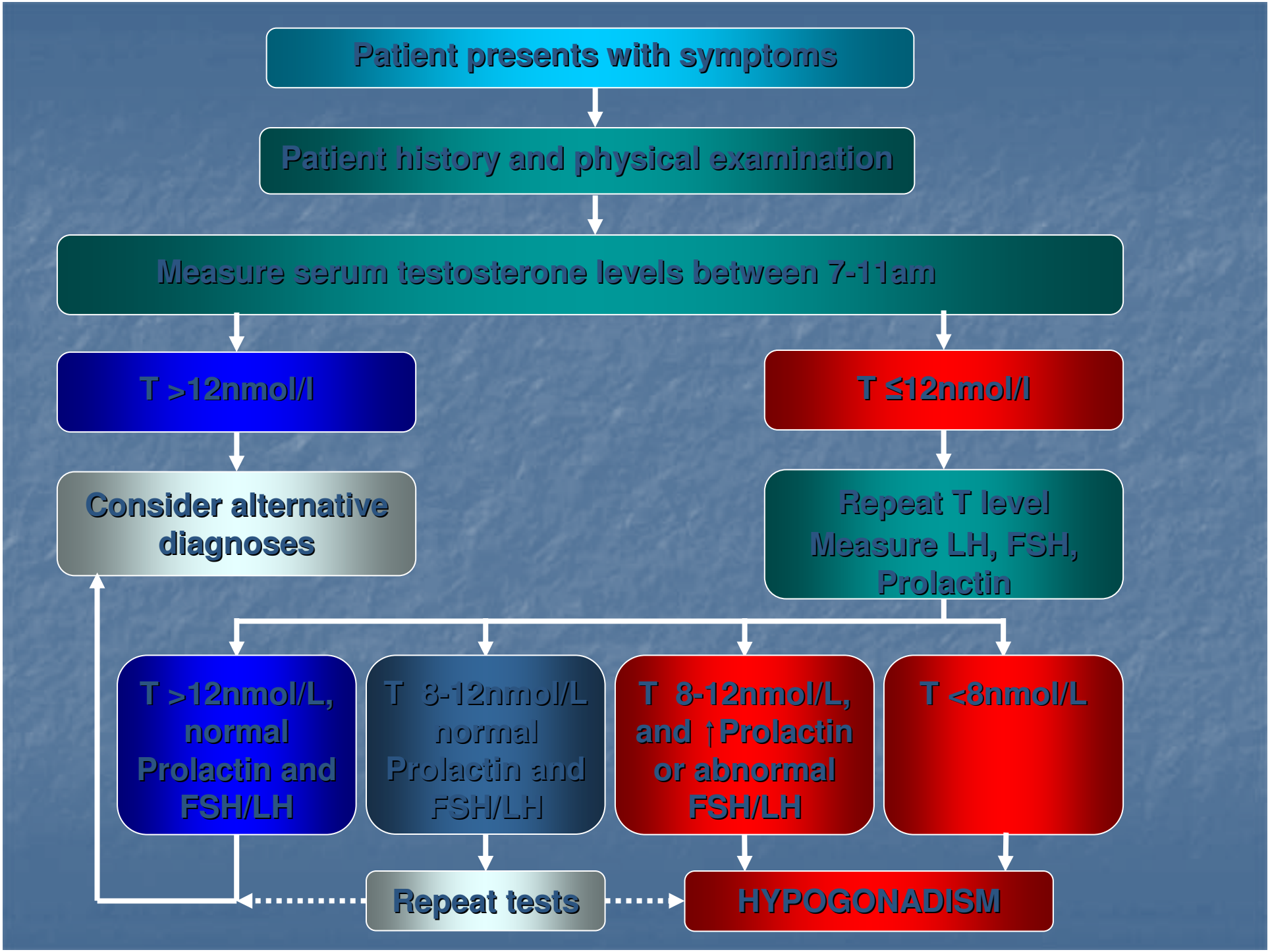
1. Nieschlag E & Behre HM. Andrology, Male reproductive health and dysfunction (2nd Edition). Springer, Heidelberg; 2002.

When should you measure testosterone?[1]

Circadian rhythm of testosterone



1. Nieschlag E & Behre HM. Andrology, Male reproductive health and dysfunction (2nd Edition). Springer, Heidelberg; 2002.


Patient presents with symptoms
Patient history and physical examination
Measure serum testosterone levels between 7-11am
T >12nmol/l
T ≤12nmol/l
Consider alternative diagnoses
Repeat T level
Measure LH, FSH, Prolactin
T >12nmol/L, normal Prolactin and FSH/LH
T 8-12nmol/L normal Prolactin and FSH/LH
T 8-12nmol/L, and ↑Prolactin or abnormal FSH/LH
T <8nmol/L
Repeat tests
HYPOGONADISM

Patients with borderline testosterone levels (8-12 nmol/l)[1,2]

- Consider additional biochemical tests
  - Gonadotrophins, SHBG, prolactin
- Careful consideration of comorbidities
- Calculate free testosterone (see online calculator at www.issam.ch/freetesto.htm)
- Counsel patient regarding treatment options

1. Nieschlag E et al. Eur Urol 2005;48:1-4.
2. Bhasin S et al. J Clin Endocrinol Metab 2006;91(6):1995-2010.

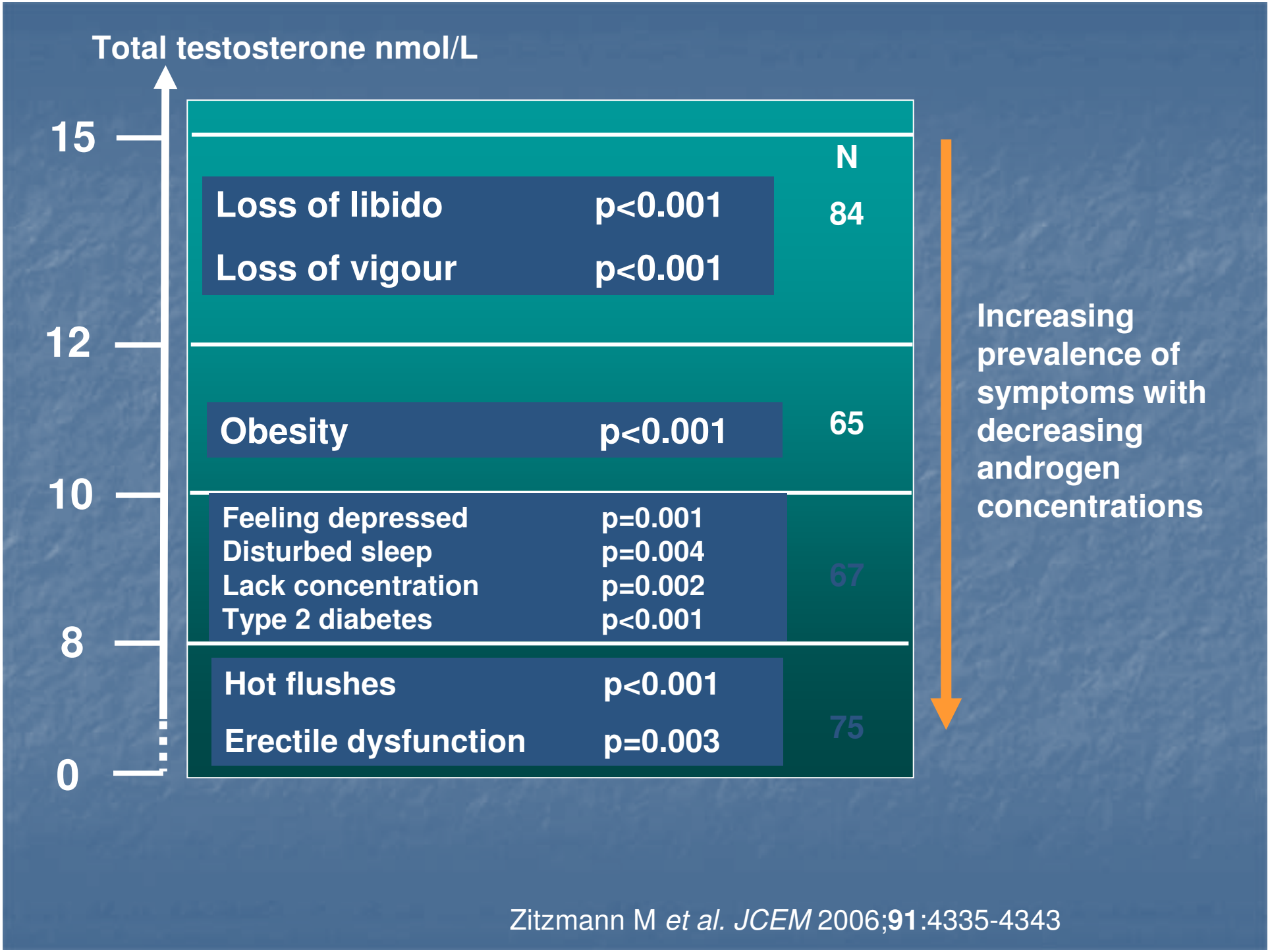
Who should receive testosterone treatment?

- Men with clinical symptoms and testosterone <8 nmol/l[1]
- Men with clinical symptoms and testosterone 8-12 nmol/l where additional investigations indicate presence of hypogonadism[1]
- Older men with significant symptoms
  - Long-term risks /benefits have yet to be clearly demonstrated

Who should receive testosterone treatment?

Contraindications to testosterone treatment

- Untreated or suspected carcinoma of prostate
- Moderate to severe symptoms of BPH
- Breast cancer
- Liver tumour
- Significant polycythaemia
- Severe cardiac failure
- Untreated sleep apnoea



Zitzmann M *et al. JCEM* 2006;**91**:4335-4343

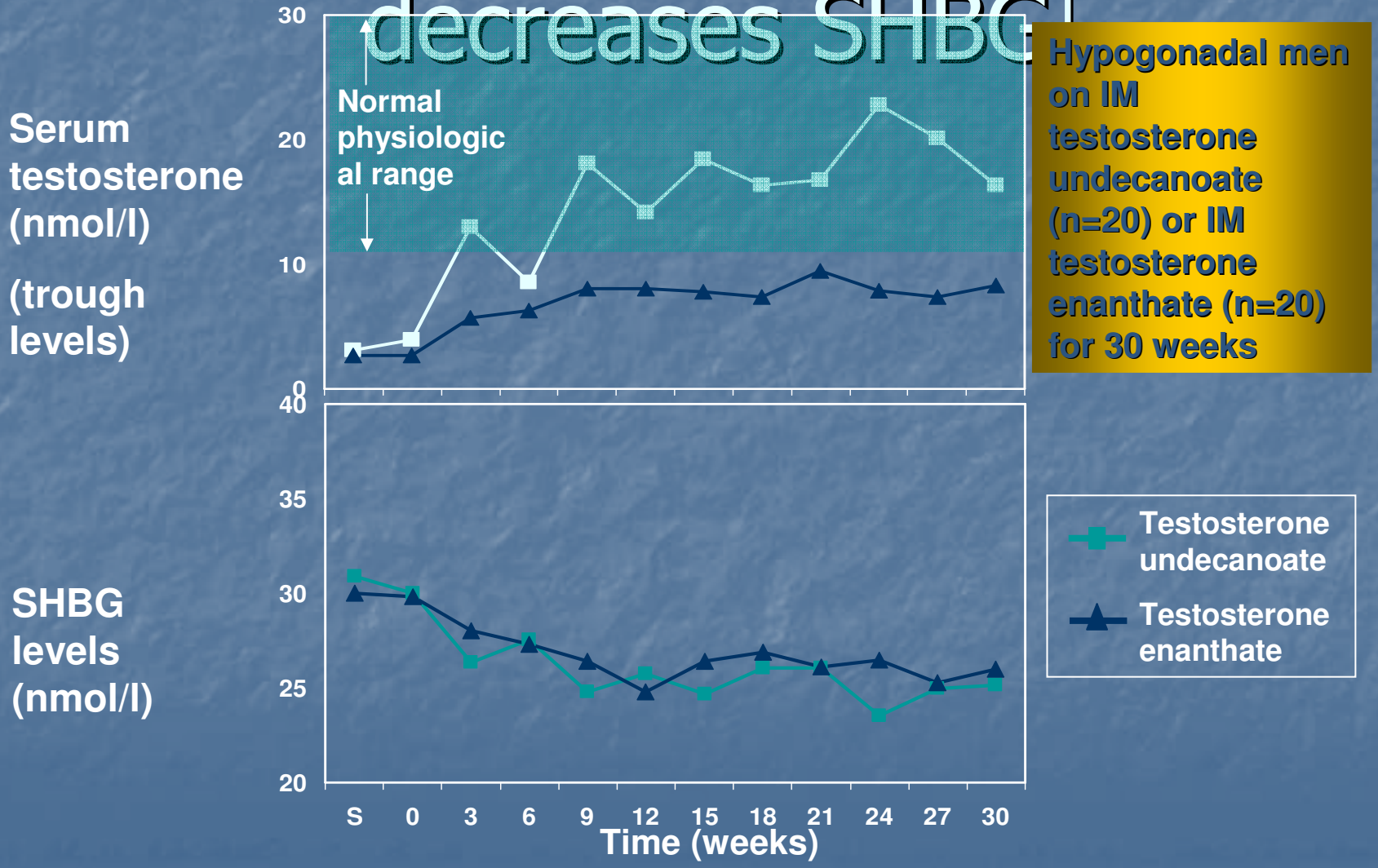
Treating hypogonadism

Goals of testosterone replacement therapy[1,2]

- Restore physiological testosterone levels
- Alleviate symptoms of androgen deficiency
- Induce or restore physiological functions
- Prevent long-term health risks of androgen deficiency

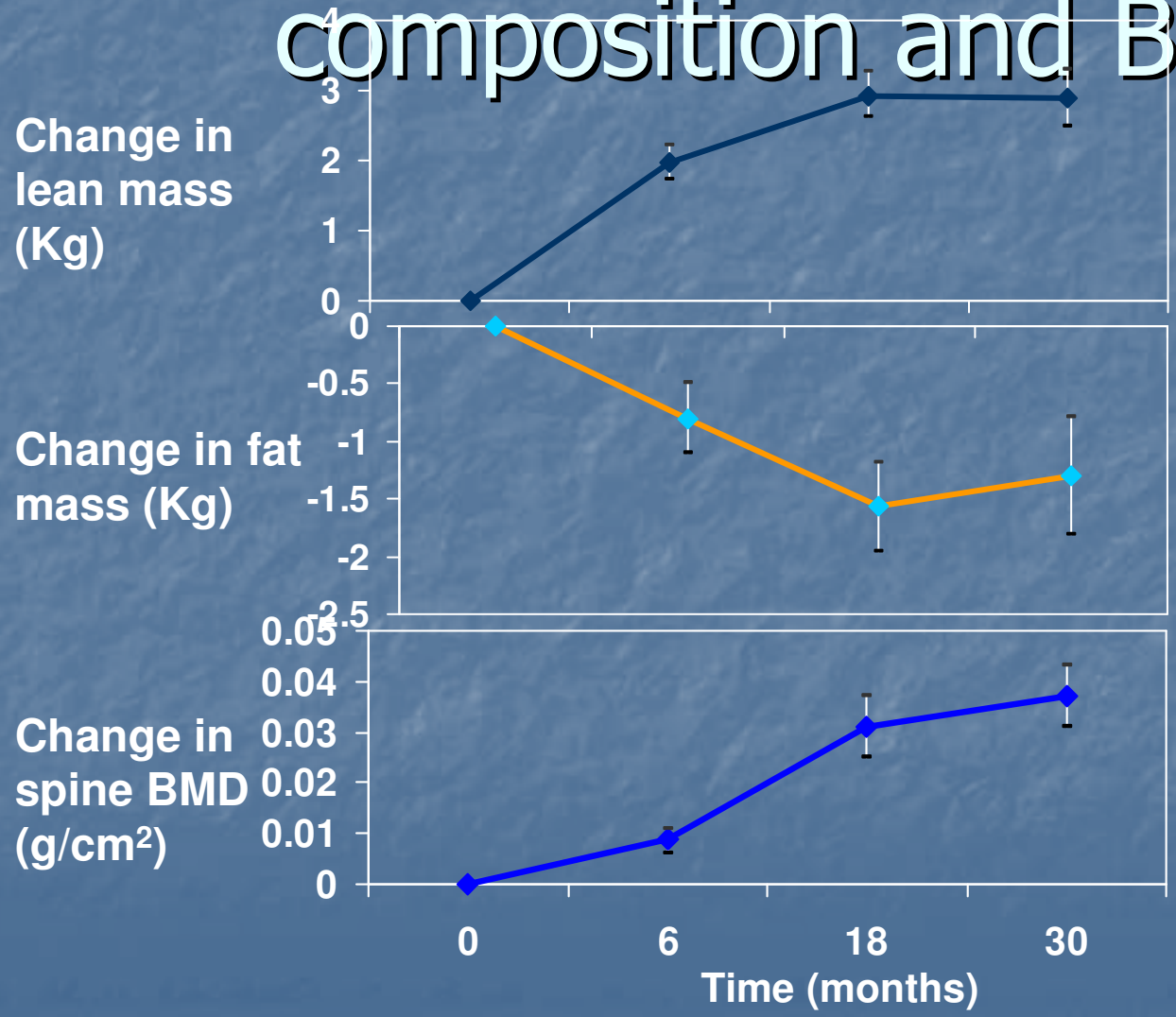
1. Nieschlag E et al. Eur Urol 2005;48:1-4.
2. Bhasin S et al. J Clin Endocrinol Metab 2006;91(6):1995-2010.

Testosterone therapy increases testosterone levels and decreases SHBG[1]



1. Huebler D et al. *Int J Impot Res* 2002;12 (Suppl.):33 (Abstract).

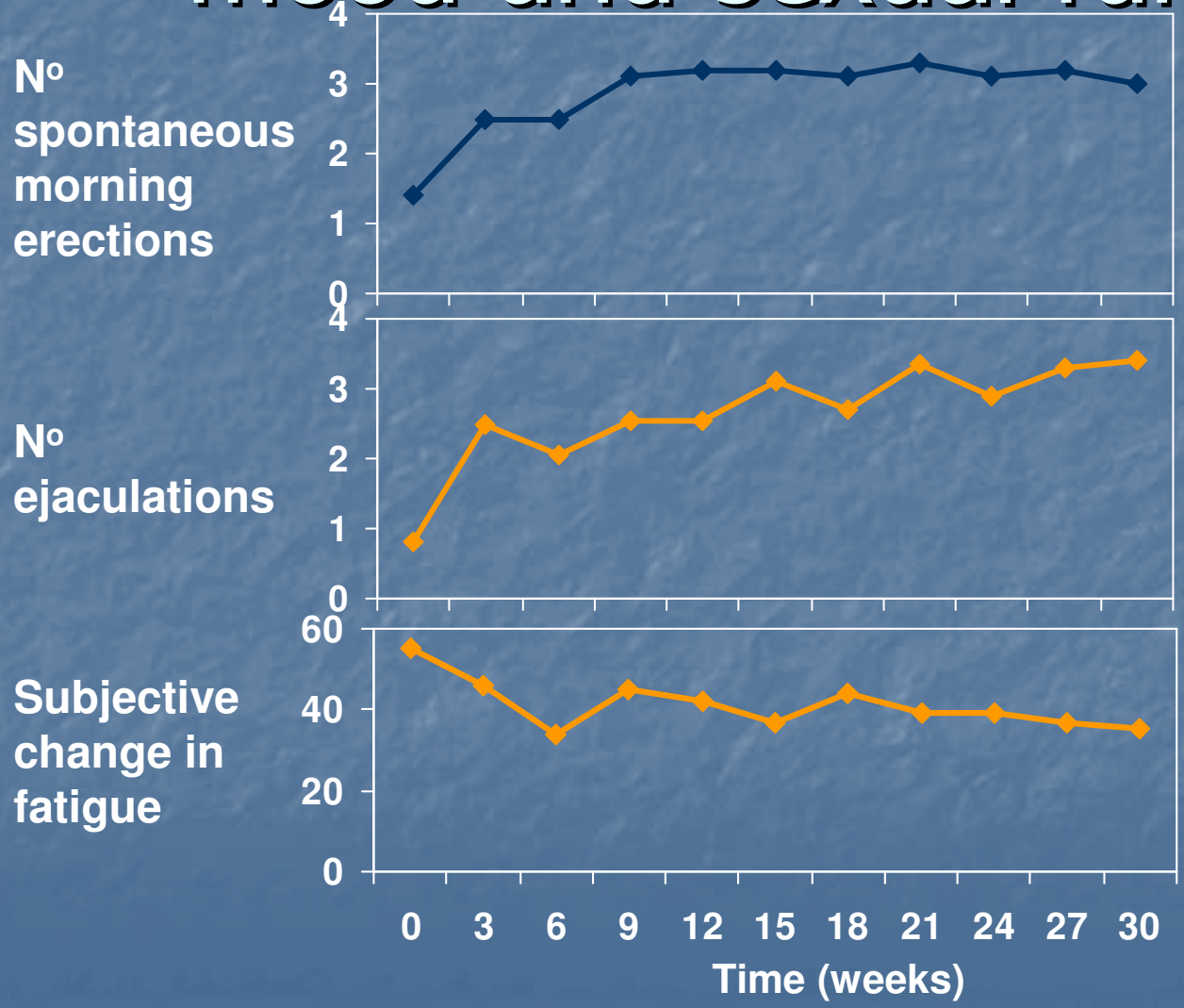
Testosterone therapy significantly improves body composition and BMD[1]



n=123 hypogonadal men receiving testosterone gel 50-100mg/day for 30 months

1. Adapted from Wang C et al. *J Clin Endocrinol Metab* 2004; 89:2085-2098.

Testosterone therapy improves mood and sexual function[1]

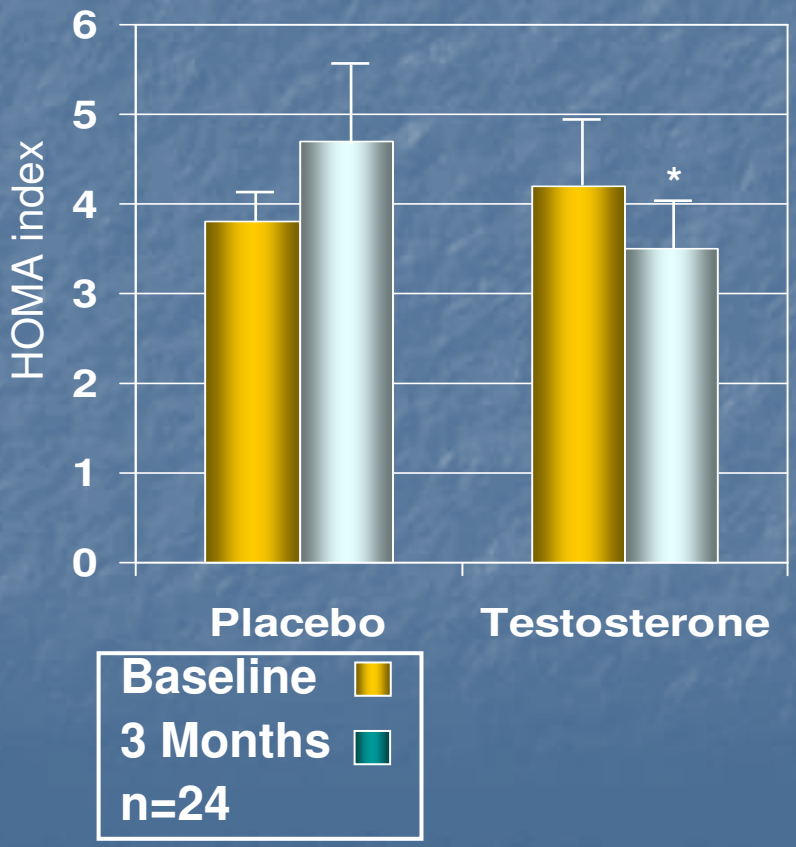


Hypogonadal men on IM testosterone undecanoate (n=20) for 30 weeks

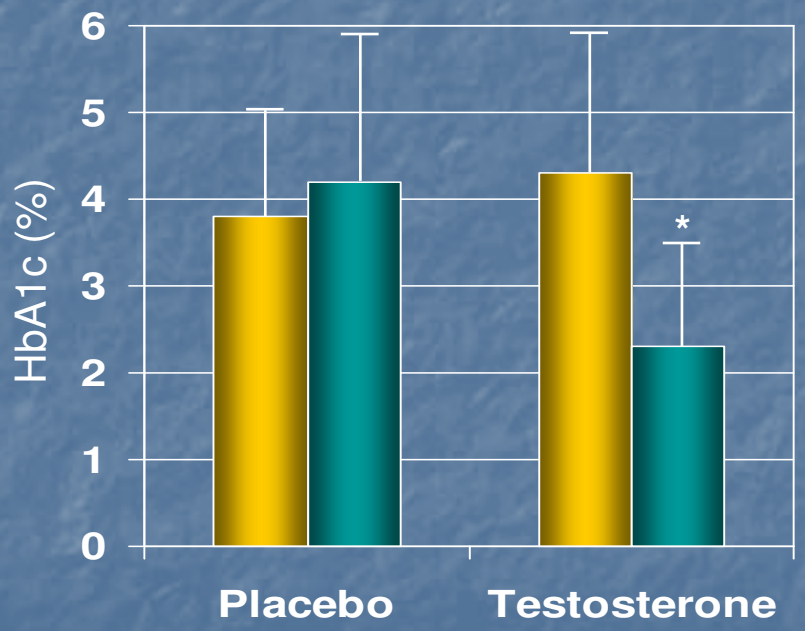
1. Rouskova D. Schering Data on file, 6 May 2002..

Testosterone therapy reduces insulin resistance in hypogonadal diabetic men[1]

A) Mean (±SEM) change in HOMA index



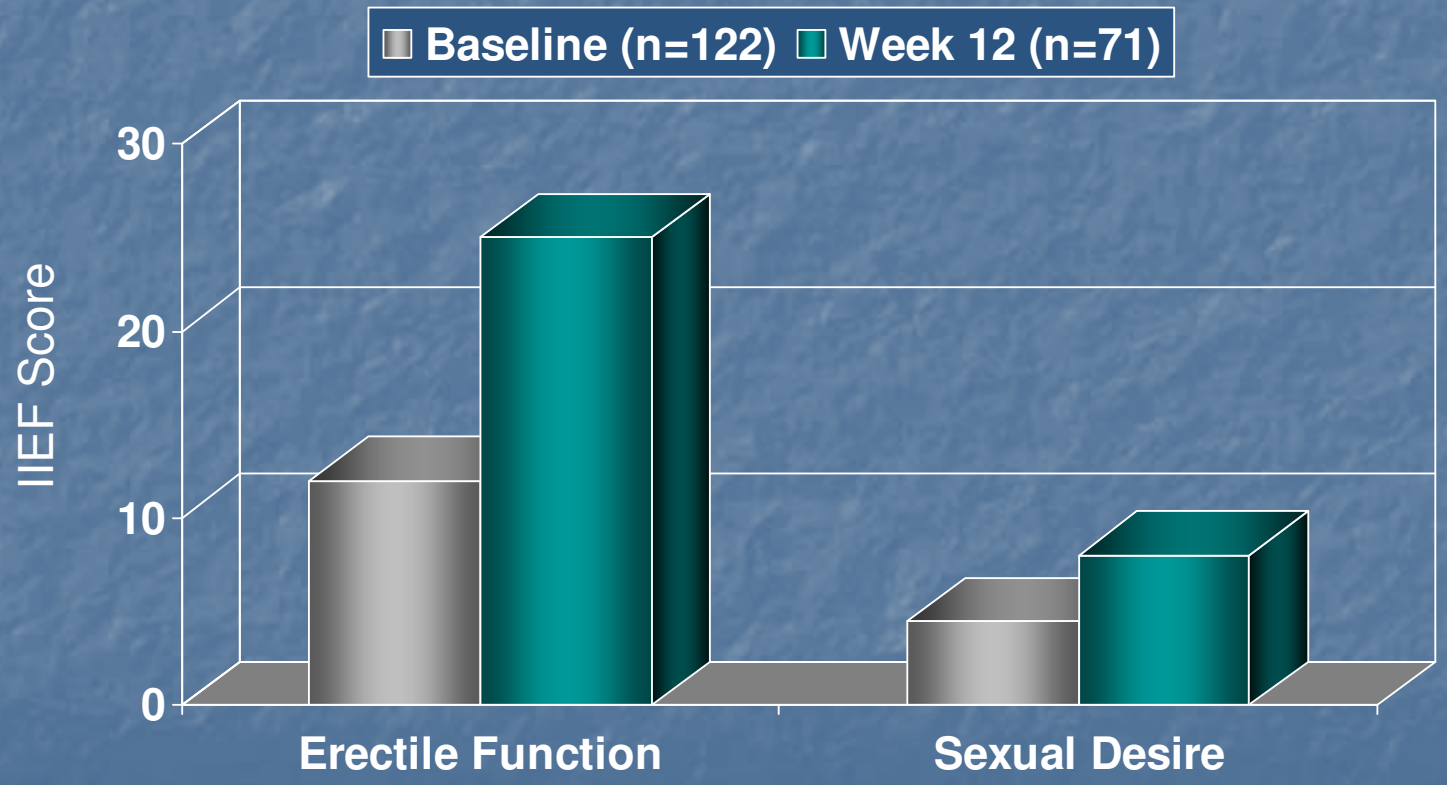
B) Mean (±SEM) change in HbA1c



*P=0.02, **P=0.003.

1. Kapoor D et al. *Eur J Endocrinol* 2006;154:899-906.

Testosterone therapy improves erectile function in hypogonadal men with ED[1]

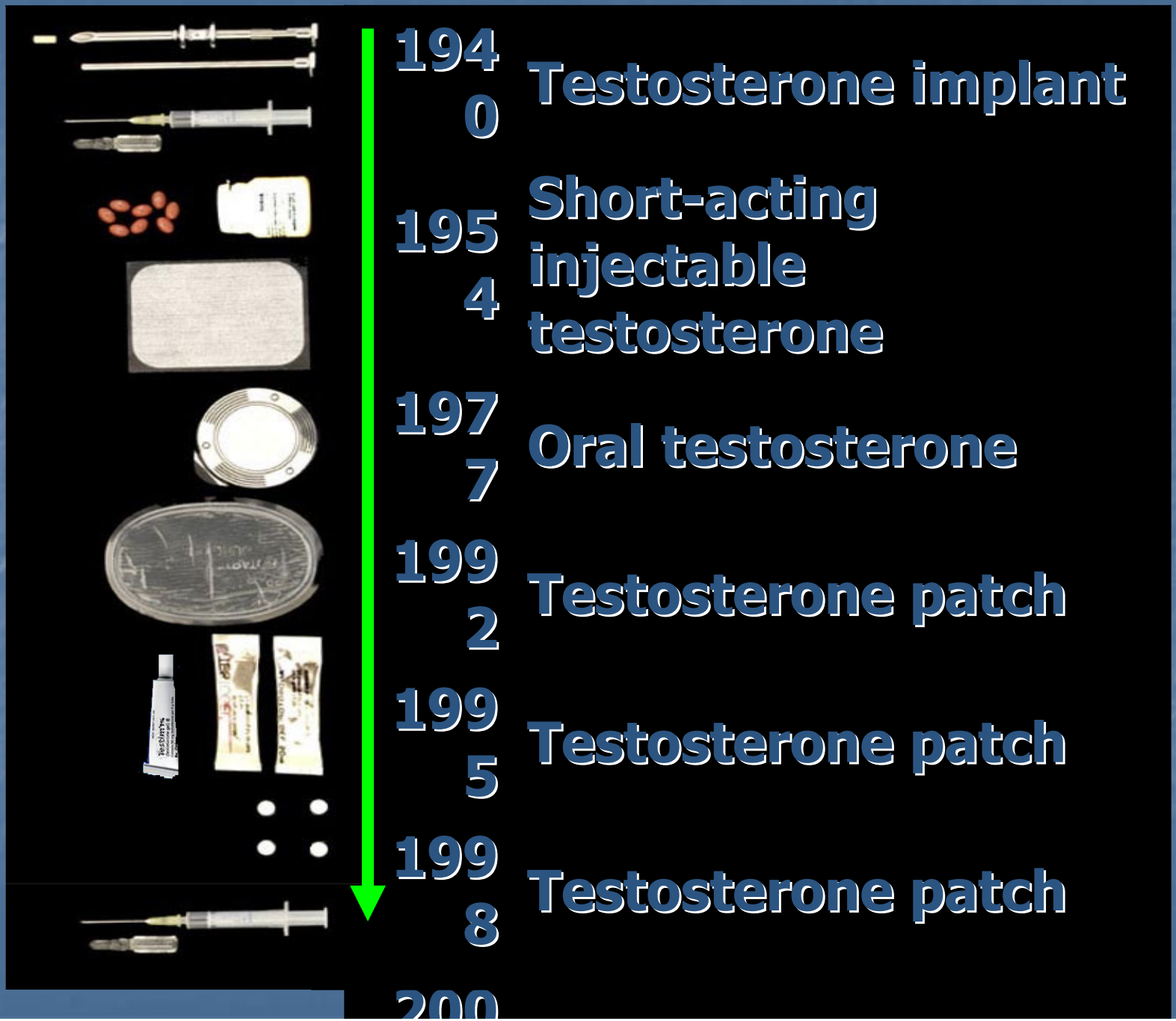


1. Yassin A et al. *World J Urol* 2006; 24:639-644.

Effects of testosterone therapy

- Endocrine
  - Increases testosterone
  - Decreases SHBG
- Physical
  - Body mass/muscle strength/BMD
- Sexual function
  - Morning erections, libido, sexual function
- Mood
  - Improved mood and cognitive function

Treatment options



1940 Testosterone implant

1954 Short-acting injectable testosterone

1977 Oral testosterone

1992 Testosterone patch

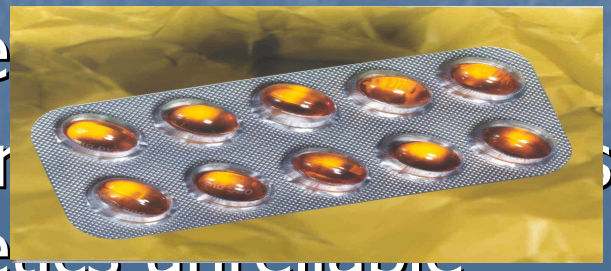
1995 Testosterone patch

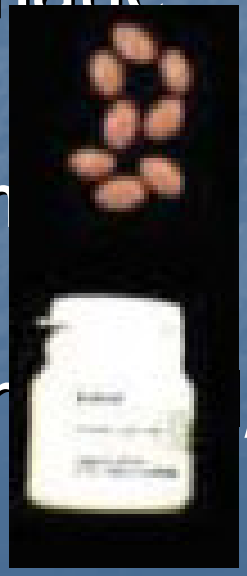
1998 Testosterone patch

2000

Oral testosterone (Restandol®;Andriol®/Testocaps™)[1,2]

- Tablets containing 40mg testosterone undecanoate as a maintenance dose taken 2-3 times a day
- Route of absorption is via lymphatic system
  - Therefore needs to taken with a r
    containing die
  - Without dietar s r , and
    pharmacokine unreliable

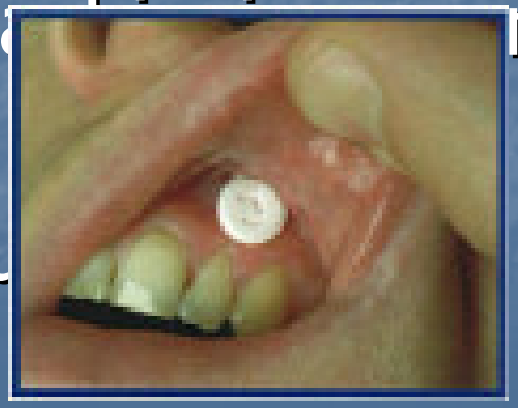




1. Nieschlag E et al. *Human Reproduct Update* 2004; 10 (5):409-419.
2. Organon Laboratories Limited. Restandol® SPC; May 1998.

Buccal testosterone[1,2] (Striant®)

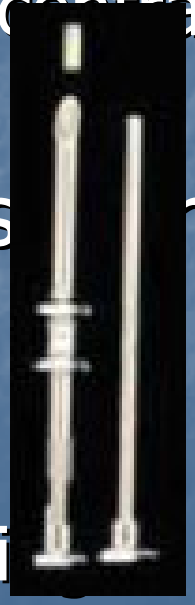
- 30mg testosterone tablet placed above incisor tooth twice daily
- Avoids hepatic inactivation
  - Absorbed across oral mucosa
- Good pharmacokinetics, [illegible]mal testosterone levels
- May be application difficu[illegible]
- Risk of site reactions



1. Nieschlag E et al. *Human Reproduct Update* 2004; 10(5):409-419.
2. Ardana Bioscience. Striant® SPC; March 2005.

Subdermal (Testosterone implants)

- Testosterone pellets (100-600mg) implanted subdermally[2]
  - Three to six pellets (600mg to 1.2g) usually maintain plasma testosterone concentrations for 4-6 months[1]
- Risk of supraphysiological testosterone levels
- Minor surgical procedure
  - Can be painful/infection risk/scarring
  - 8.5% extrusion of pellets[3]



1. Nieschlag E et al. *Human Reproduction Update* 2004; 10(5): 409-419.
2. Organon Laboratories Limited. Testosterone Implant 200mg SPC; May 1999.
3. Handelsman DJ et al. *Clin Endocrinol* 1997;47:311-316.

Transdermal patches[1,2] (e.g. Andropatch®)

- 2.5-7.5mg testosterone delivered, starting dose
- Daily circadian profile of testosterone delivery[3,4]
- Alcohol base to enhance permeation
- Skin reactions common (>50% patients)[3,4]
- Size of patch can be obtrusive
- May make crinkling noise

1. Nieschlag E et al. *Human Reproduct Update* 2004; 10(5):409-419.
2. GlaxoSmithKline UK. Andropatch® 5mg SPC; August 2002.
3. Wang C et al. *J Clin Endocrinol Metab* 2000; 85(8):2839-2853.
4. Gooren LJG et al. *Drugs* 2004;64(17):1861-1891.

Transdermal gels[1,2,3] (Testogel®; Testim®)

- 50-100 mg testosterone gel applied each morning to shoulders, back, or abdomen
- Daily circadian profile of testosterone delivery[2,4]
- Skin reactions in 4-10% patients[2,3]
- Avoid washing for 6 hours
- Risk of transfer to another per skin contact
- Daily patient compliance required

1. Nieschlag E et al. *Human Reproduct Update* 2004; 10(5):409-419.
2. Schering Health Care Limited. Testogel ® 50mg SPC; February 2004.
3. Ipsen Ltd. Testim ® 50mg SPC; August 2004.
4. Wang C et al. *J Clin Endocrinol Metab* 2000; 85(8):2839-2853.

Intramuscular injections – short acting[1,2] (Sustanon® 100; Sustanon® 250; Testoviron®)

- Currently the most widely used form of testosterone
- Two short-acting preparations widely available in UK
  - Sustanon 100 (testosterone: propionate/phenylpropionate/ isocaproate in arachis oil)
  - Sustanon 250 (testosterone: propionate/phenylpropionate/ isocaproate/decanoate in arachis oil)
- Injection every 2 weeks (Sustanon 100) or 3 weeks (Sustanon 250)[2,3]

1 Nieschlag E et al. *Human Reproduct Update* 2004; 10(5):409-419.
2. Organon Laboratories Limited. Sustanon® 100 SPC; February 2004
3. Organon Laboratories Limited. Sustanon® 250 SPC; January 2006.

Intramuscular injections - long acting[1] (Nebido®)

- 1000 mg testosterone undecanoate in 4 ml castor oil
- Loading dose at 6 weeks, and then every 10 to 14 weeks[1]
- Testosterone levels maintained within the physiological range[2]
  - Avoids frequent peaks and troughs in testosterone levels that may b[illegible]h short acting injections[3]

- Increased patient convenience (quarterly

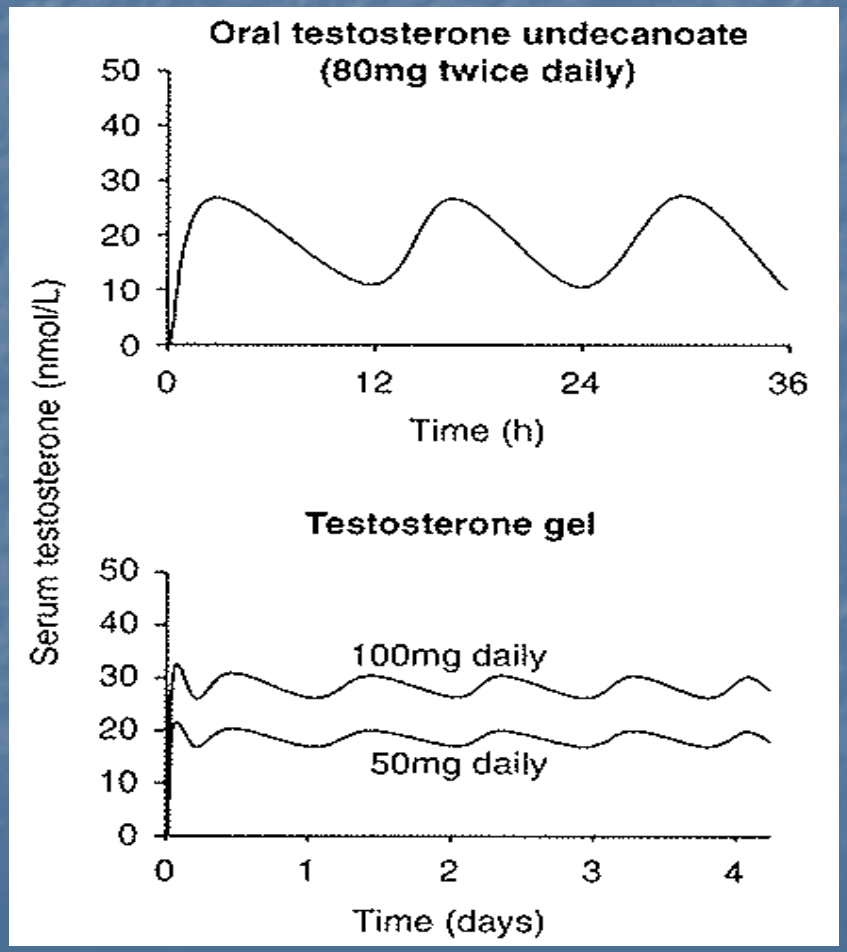
1. Schering Healthcare Limited. Nebido® SPC. October 2004.
2.Von Eckardstein S et al. *J Androl* 2002;23(3):419-425.
3.Schubert M et al. *J Clin Endocrinol Metab* 2004;89:5429-5434.

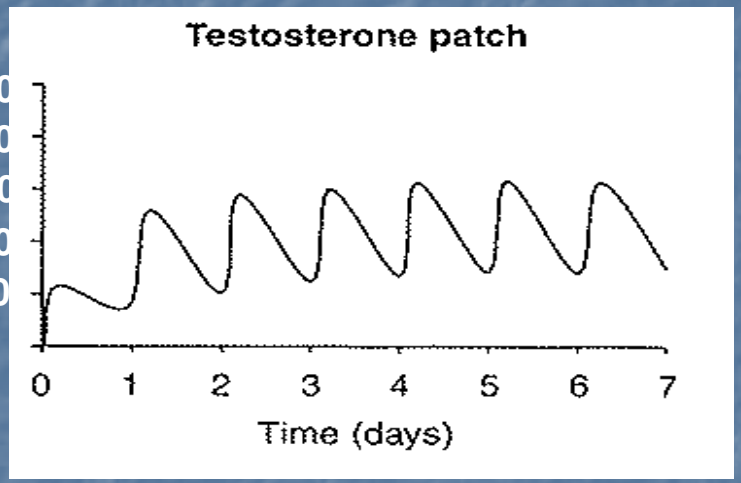
Testosterone therapy

- Number of testosterone preparations available
- Differ by route of application
- Patient choice and satisfaction important
- Patients should be provided with sufficient information to enable them to make an informed decision regarding suitable therapy

Pharmacokinetics of different testosterone preparations

Pharmacokinetics: daily testosterone preparations[1]

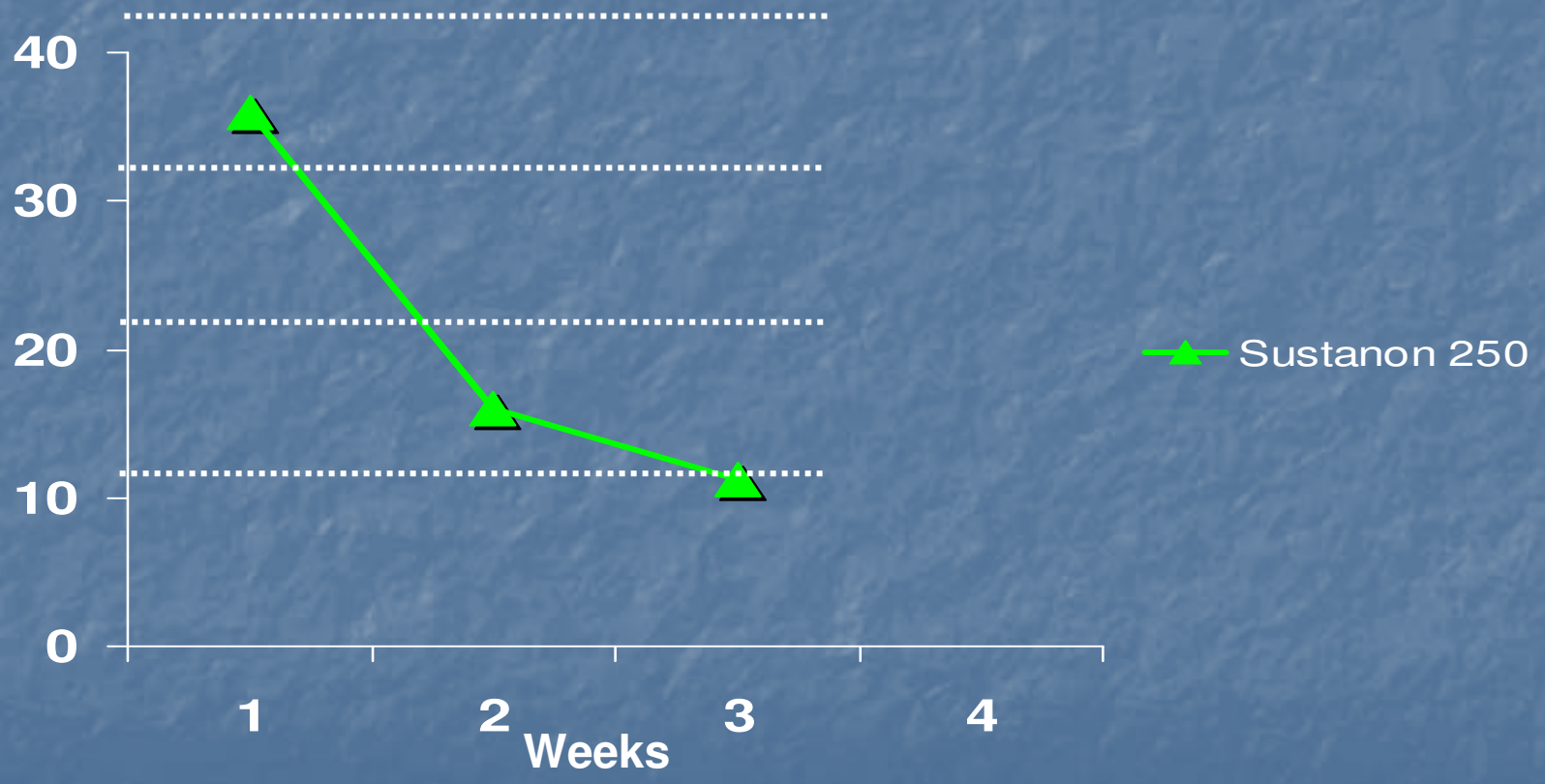




Note the different timescales on these graphs

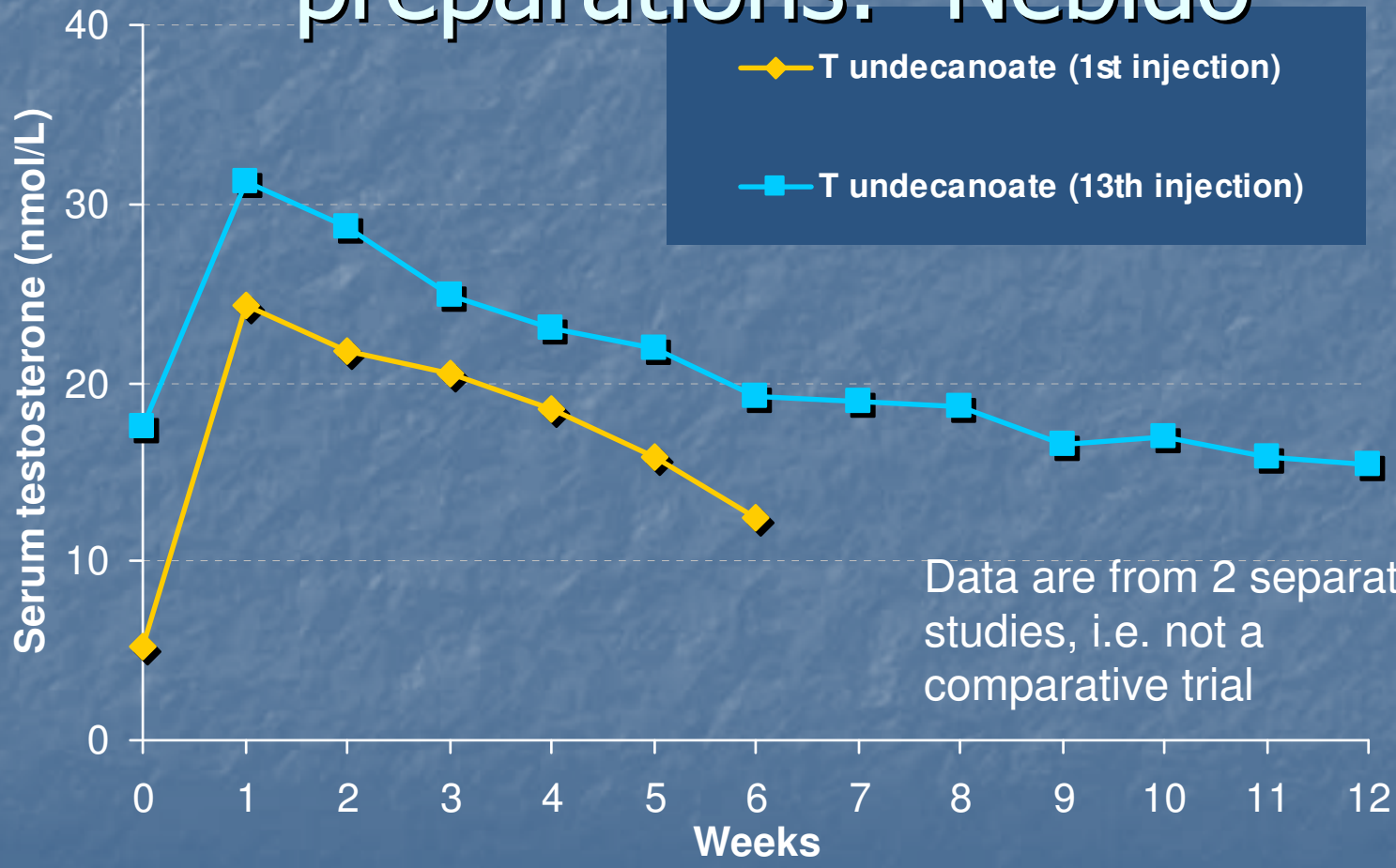
1. Gooren LJG et al. *Drugs* 2004.64(17):1861-1891.

Pharmacokinetics of UK available injectable testosterone preparations: Sustanon 250[1]



1. Lane HA et al. *Endocrine Abstracts* 2006;11:P677.

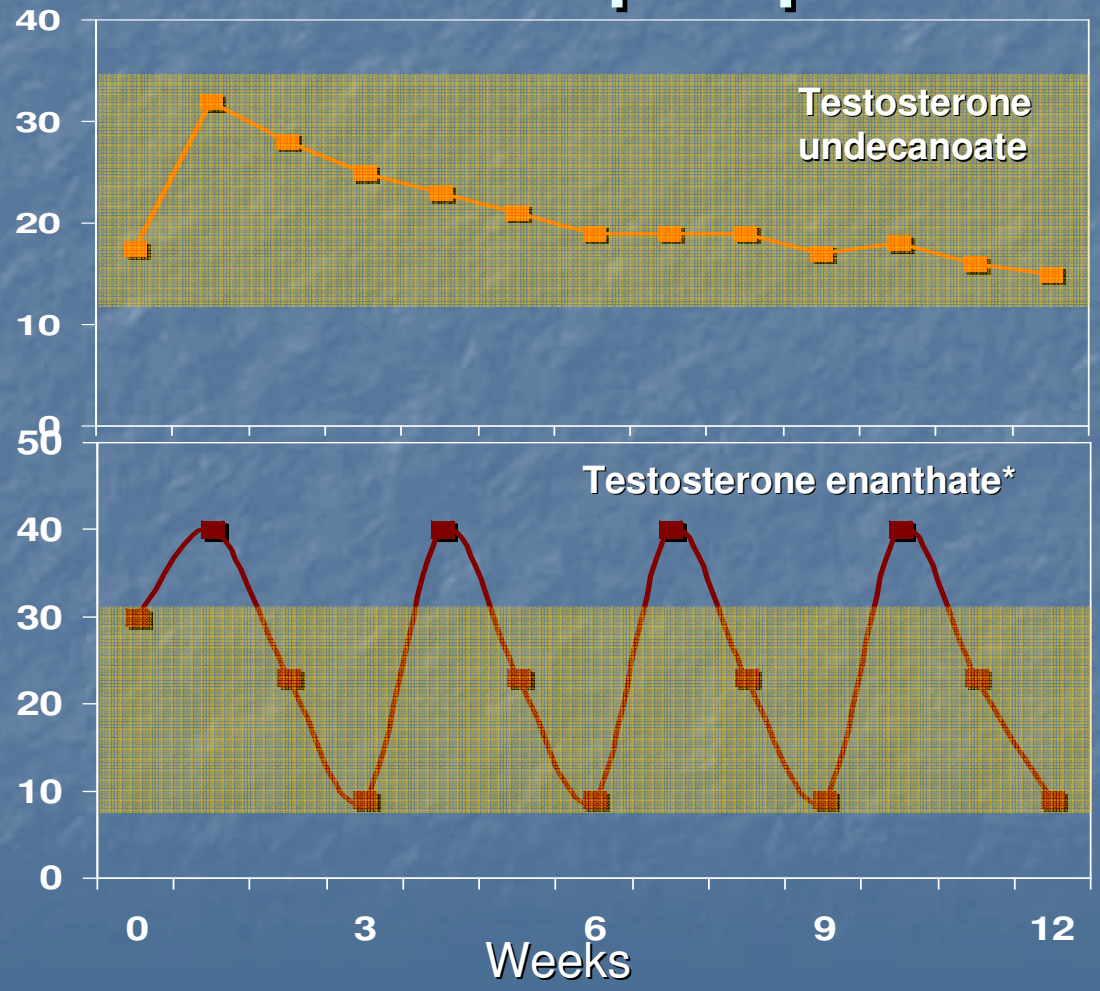
Pharmacokinetics of UK available injectable testosterone preparations: Nebido[1-3]



Data are from 2 separate studies, i.e. not a comparative trial

1. Von Eckardstein S et al. *J Androl* 2002; 23(3):419-425.
2. Behre HM et al. *Eur J Endocrinol* 1999;140:414-419.

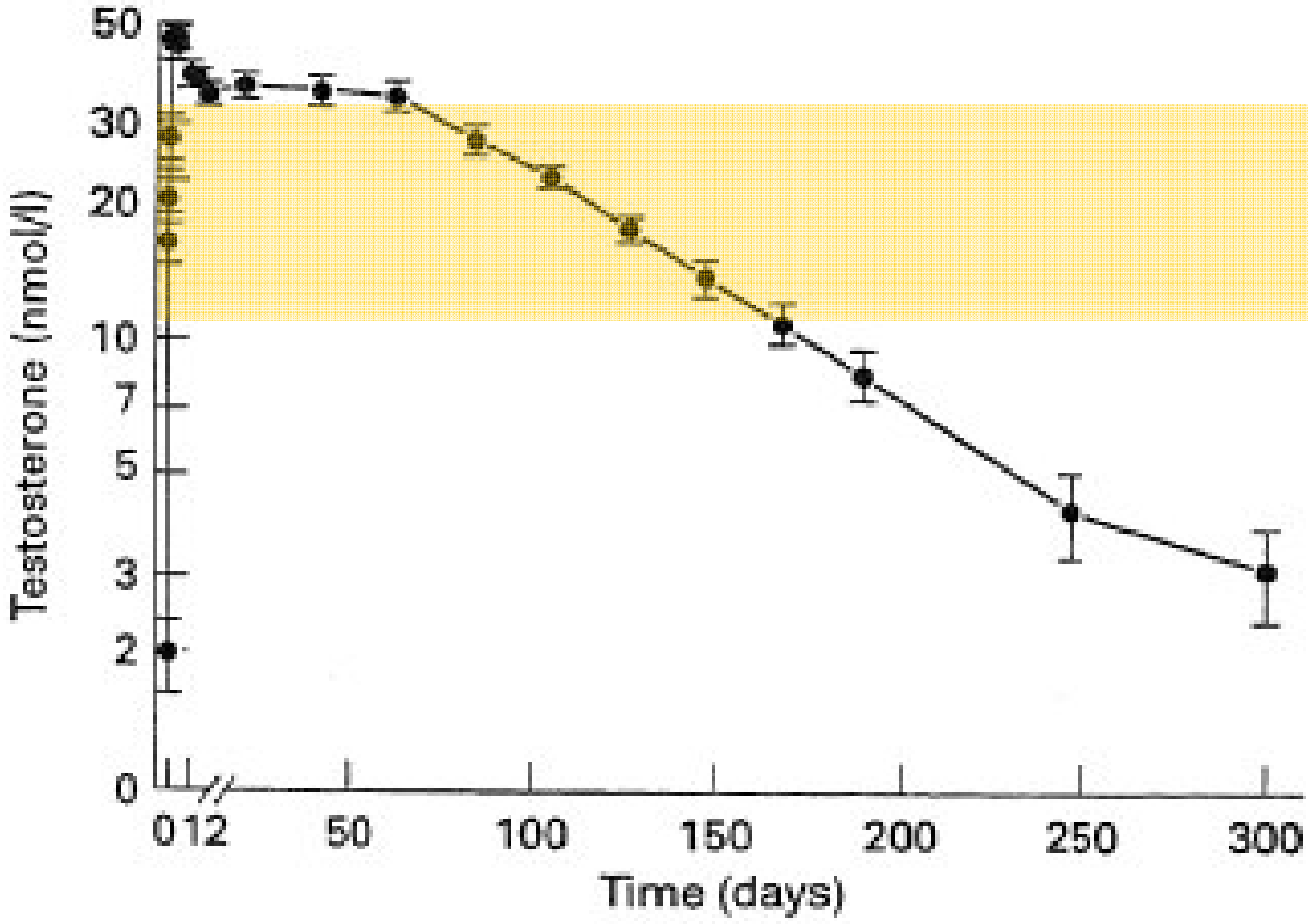
Pharmacokinetics: Injectable testosterone preparations[1,2]



1. Gooren LJG et al. *Drugs* 2004.64(17):1861-1891.
2. Von Eckardstein S et al. J Androl 2002; 23(3):419-425.

*Simulated data

Pharmacokinetics: testosterone implants



1. Jockenhovel F et al. *Clin Endo* 1996;45:61-71.

Monitoring patients on testosterone therapy

Areas of potential concern[1,2]

- Prostate
- Cardiovascular
- Behavioural changes
  - Personality changes

1. Nieschlag E et al. *Eur Urol* 2005;48:1-4.
2. Bhasin S et al. *J Clin Endocrinol Metab* 2006;91(6):1995-2010.

Parameters to monitor or to be aware of during therapy[1,2]

- Prostate
- Haematocrit and haemoglobin
  - Increased levels particularly associated with supraphysiological levels of testosterone
- Blood lipids
- Liver function
- Miscellaneous adverse effects of testosterone
  - E.g. gynaecomastia, acne, oily skin, priapism,

1. Bhasin S et al. *J Clin Endocrinol Metab* 2006;91(6):1995-2010.
2. Nieschlag E et al. *Human Reproduct Update* 2004; 10(5):409-419.

Endocrine Society: recommendations[1]

Parameter	Baseline	3 month	Annual
PSA	Y	Y	Y
DRE	Y	Y	Y
Haematocrit	Y	Y	Y
Testosterone	-	Y	Y
BMD	Y	-	Y

1. Bhasin S et al. *J Clin Endocrinol Metab* 2006;91(6):1995-2010.

PSA levels

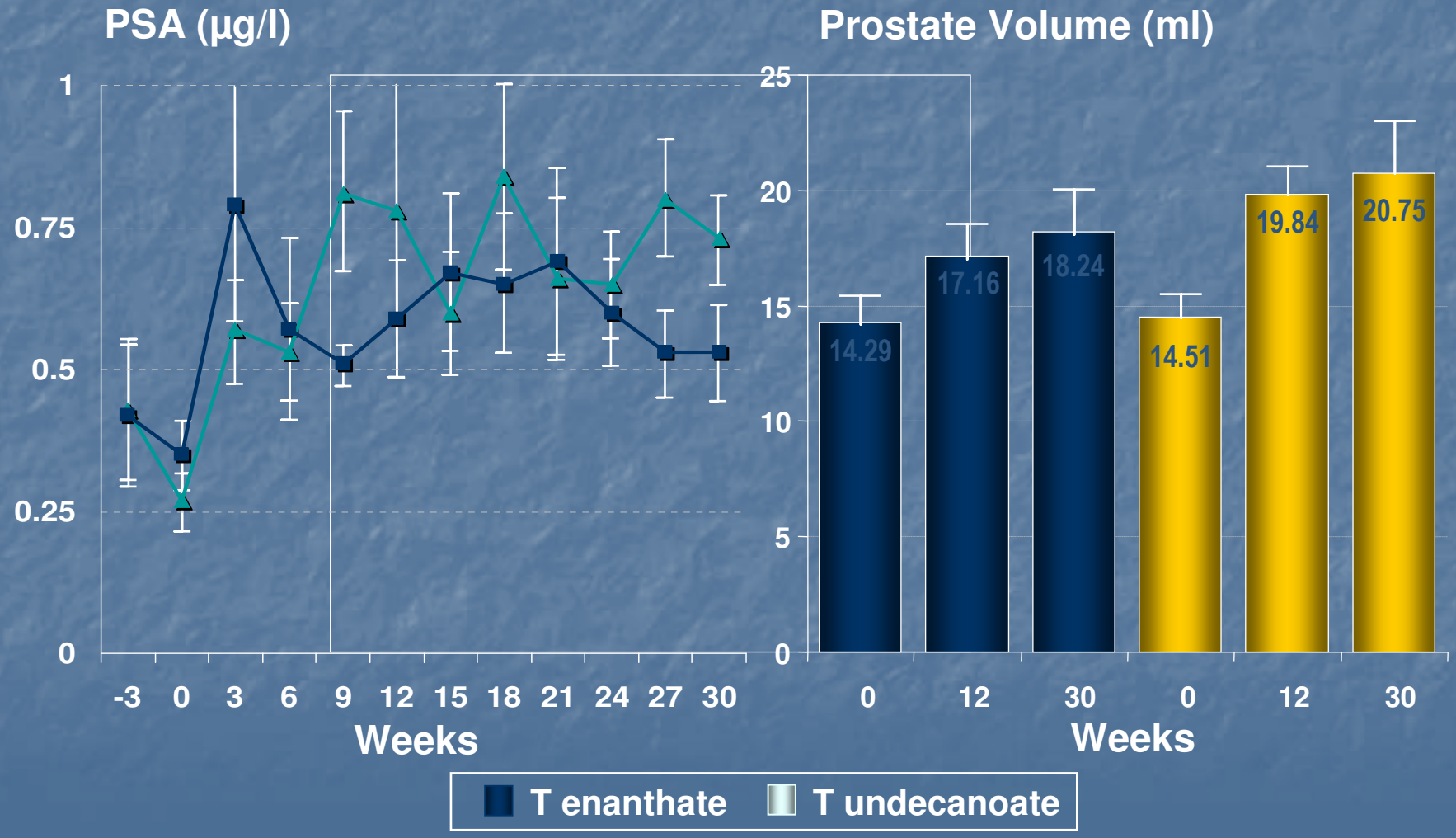
- PSA = screening test for prostate cancer
- PSA increases with age
- Increase in accepted PSA cut-off with age
  - 40-49 years 2.5 ng/ml
  - 50-59 years 3.5 ng/ml
  - 60-69 years 4.5 ng/ml
  - Over 70 years 6.5 ng/ml

Endocrine Society: Prostate monitoring[1]

- Urological consultation should be sought if there is:
  - Verified PSA >4.0 ng/ml
  - Increase in PSA concentration >1.4ng/ml within any 12-month period of testosterone treatment
  - PSA velocity >0.4ng/ml/year
  - Detection of a prostatic abnormality on DRE

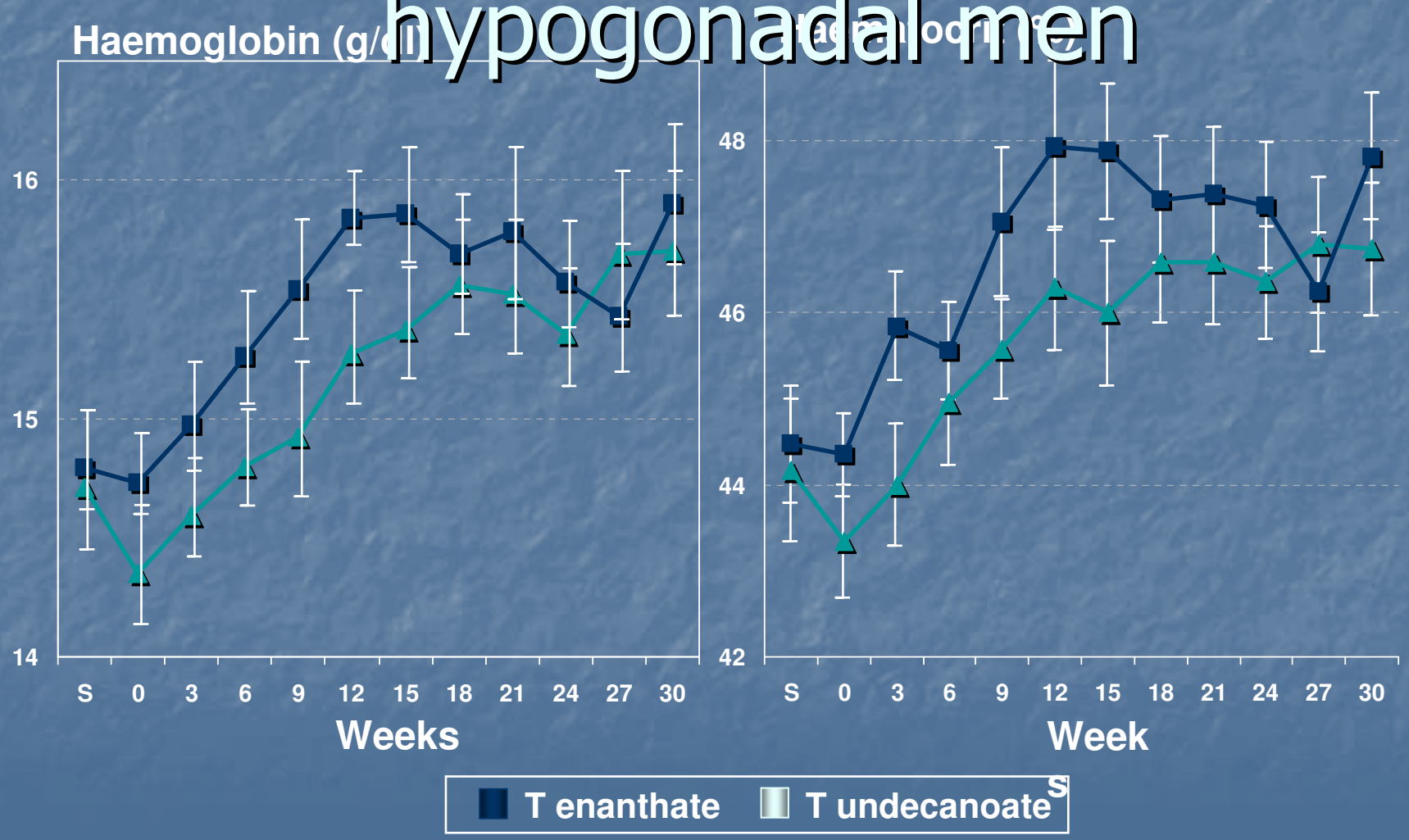
1. Bhasin S et al. *J Clin Endocrinol Metab* 2006;91(6):1995-2010.

PSA and prostate volume during testosterone treatment



1. Huebler D et al. *Endo 2000* Abstract Book: 567.

Erythropoiesis under testosterone treatment in 40 hypogonadal men



1. Huebler D et al. *Endo 2000* Abstract Book: 567.

Conclusion (1)

- Testosterone influences sexual, metabolic and psychological functions
- Male hypogonadism is inadequate functioning of the testes, characterised by abnormally low testosterone levels
- Male hypogonadism is associated with increasing age, ED, type 2 diabetes and abdominal obesity
- Diagnosis of hypogonadism is based on clinical features with biochemical confirmation

Conclusion (2)

- Testosterone therapy increases circulating testosterone levels with significant symptom improvement
  - Treatment decision based on compliance, convenience, choice
  - Monitor: prostate/haematocrit/clinical response
- Testosterone therapy provides significant improvement in quality of life for patients with male hypogonadism

NEBIDO PRESCRIBING INFORMATION 1

Nebido® (testosterone undecanoate)
Presentation: Ampoule with 4ml solution for injection containing 1000mg testosterone undecanoate.
Uses: Testosterone replacement therapy for male hypogonadism when testosterone deficiency confirmed by clinical features and biochemical tests.
Dosage: One ampoule (1000mg) injected intramuscularly every 10 to 14 weeks. *Starting treatment:* Measure serum testosterone levels before start and during initiation of treatment. If appropriate, first injection interval may be reduced to a minimum of 6 weeks. *Maintenance:* Injection interval within 10 to 14 week range. Monitor serum testosterone regularly; adjust injection interval as appropriate.
Children: Not for use in children. **Not evaluated clinically in males under 18.**
Contra-indications: Androgen-dependent prostate cancer or breast cancer. Past or present liver tumours. Hypersensitivity to testosterone or any of the excipients.
Warnings and precautions: Limited experience in patients over 65. **Before therapy exclude prostate cancer. Examine prostate and breast at least annually, or twice yearly in elderly or at risk patients (clinical or familial factors). Periodically check testosterone concentrations, haemoglobin, haematocrit, liver function. Androgens may accelerate the progression of sub-clinical prostate cancer and benign prostatic hyperplasia. Monitor serum calcium concentrations in cancer patients at risk of hypercalcaemia (and hypercalcinuria). Rarely, liver tumours have been reported.**
Nebido may cause oedema with or without congestive cardiac failure in patients with severe cardiac, hepatic or renal insufficiency or ischaemic heart disease. In this case, stop treatment immediately. Use with caution in patients with renal or hepatic impairment, epilepsy, migraine or blood clotting irregularities. Improved insulin sensitivity may occur.
Irritability, nervousness, weight gain, prolonged or frequent erections may indicate excessive androgen exposure requiring dose adjustment. Withdraw treatment if these symptoms persist or reappear. Pre-existing sleep apnoea may be potentiated.
Testosterone may produce a positive reaction in anti-doping tests. Not for use in women. Not suitable for developing muscles or increasing fitness in healthy individuals. Inject Nebido extremely slowly to avoid the coughing or respiratory distress reactions that occur rarely with injection of oily solutions.
Interactions reported with oral anticoagulants (requires dose monitoring), ACTH or corticosteroids, and thyroxin binding globulin in laboratory tests.

NEBIDO PRESCRIBING INFORMATION 2

Side-effects: Most common reactions are injection site pain (10%). Also reported are: diarrhoea; leg, breast or testicular pain; arthralgia; dizziness; increased sweating; headache; respiratory, skin or prostate disorders; acne; gynaecomastia; pruritus; subcutaneous haematoma at injection site. Other known reactions to testosterone containing preparations are: polycythaemia (erythrocytosis); weight gain; electrolyte changes; muscle cramps; nervousness, hostility, depression; sleep apnoea; very rarely jaundice and liver function test abnormalities; skin reactions; libido changes; increased frequency of erections; interruption or reduction in spermatogenesis; priapism; prostate abnormalities; prostate cancer (inconclusive data); urinary obstruction; water retention; oedema; hypersensitivity.

Basic NHS Price: £76.70 per 1 x 4ml

Legal Classification: POM

Product Licence Number: 0053/0350

Product Licence Holder: Schering Health Care Ltd.,
The Brow,
Burgess Hill,
West Sussex RH15 9NE

Nebido is a registered trademark of Bayer Schering Pharma AG (formerly Schering AG)

PI revised: 28 June 2007

Information about adverse reaction reporting in the UK can be found at www.yellowcard.gov.uk. Alternatively, adverse reactions can be reported to Bayer plc by email: phdsguk@bayer.co.uk

TESTOGEL PRESCRIBING INFORMATION 1

Testogel® (testosterone)
Presentation: Sachet containing 50mg testosterone in 5g colourless gel.
Uses: Testosterone replacement therapy for male hypogonadism when testosterone deficiency confirmed by clinical features and biochemical tests.
Dosage: One 5g gel sachet daily. **Can be adjusted in 2.5g gel steps, to a maximum of 10g gel daily. Once sachet opened, apply immediately onto clean, dry healthy skin over both shoulders, or both arms or abdomen. Do not apply to genital areas.**
Children: Not for use in children. **Not evaluated clinically in males under 18.**
Contra-indications: Known or suspected prostate or breast cancer. **Hypersensitivity to testosterone or any constituents of the gel.**
Warnings and precautions: Before therapy exclude prostate cancer. Examine prostate and breast at least annually, or twice yearly in elderly or at risk patients (clinical or familial factors). Monitor serum calcium concentrations in cancer patients at risk of hypercalcaemia (and hypercalcinuria). Testogel may cause oedema with or without congestive cardiac failure in patients with severe cardiac, hepatic or renal insufficiency. In this case, stop treatment immediately. Use with caution in patients with ischaemic heart disease, hypertension, epilepsy and migraine. Periodically check testosterone concentrations, haemoglobin, haematocrit, liver function (tests), lipid profile.
Possible increased risk of sleep apnoea especially if obesity or chronic respiratory disease present.
Improved insulin sensitivity may occur.
Irritability, nervousness, weight gain, prolonged or frequent erections may indicate excessive androgen exposure requiring dose adjustment.
If severe application site reactions occur, discontinue if necessary. Testosterone may produce a positive reaction in anti-doping tests. Not for use in women.
Testosterone gel can be transferred to others by close skin to skin contact and can lead to adverse effects (inadvertent androgenisation) if repeated contact. Inform patient of transfer risk that is prevented by clothing or washing of application site. Testogel should not be prescribed for patients who may not comply with safety instructions (e.g. alcoholics, drug abusers, psychiatric patients).
Pregnant women must avoid any contact with the application sites.
Interactions reported with oral anticoagulants, ACTH or corticosteroids, and thyroxin binding globulin in laboratory tests.

TESTOGEL PRESCRIBING INFORMATION 2

Side-effects: Most common (10%) were: skin reactions. Also reported were: changes in laboratory tests (polycythaemia, lipids), headache, prostatic disorders, gynaecomastia, mastodynia, dizziness, paraesthesia, amnesia, hyperaesthesia, mood disorders, hypertension, diarrhoea, alopecia, urticaria. Other known reactions to testosterone treatments are: muscle cramps; nervousness; depression; hostility; sleep apnoea; skin reactions; libido changes; more frequent erections; hypersensitivity reactions; rarely: jaundice, liver function tests, priapism, prostate abnormalities, prostate cancer (inconclusive), urinary obstruction. During high dose and/or prolonged treatment: weight gain, electrolyte changes, reversible interruption or reduction of spermatogenesis, water retention, oedema, rarely hepatic neoplasms. Frequent applications may cause irritation and dry skin.

Basic NHS Price: £33.00 per pack of 30 x 5g sachets
Legal Classification: POM
Product Licence Number: 16468/0005
Product Licence Holder: Laboratoires BESINS INTERNATIONAL
5, rue du Bourg L'Abbé
75003 Paris
France
Distributed by: Schering Health Care Ltd.,
The Brow,
Burgess Hill,
West Sussex RH15 9NE
Testogel is a registered trademark of Laboratoires BESINS INTERNATIONAL
PI revised: 4 July 2007

Information about adverse reaction reporting in the UK can be found at www.yellowcard.gov.uk. Alternatively, adverse reactions can be reported to Bayer plc by email: phdsguk@bayer.co.uk