Testosterone deficiency in men with T2DM – highlighting the benefits of testosterone therapy

Dr Jonny Coxon MA MD MRCS MRCGP FECSM
GP Partner
Special Interest in Sexual Medicine
Clinical Assistant roles: Urology & Gender Identity

Men's Health Matters

This educational symposium is organised and funded by Bayer and contains promotional content

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Tel: 01182063500, Fax: 01182063703
Email: pvuk@bayer.com

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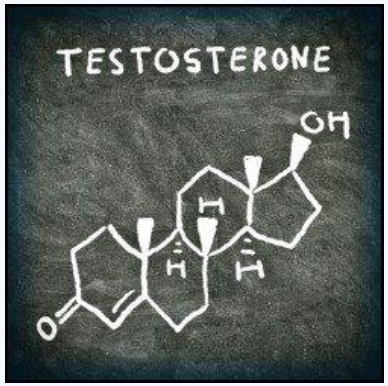
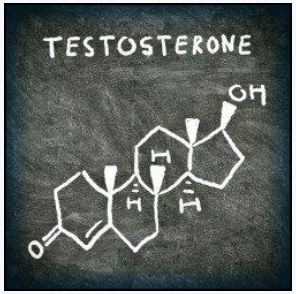
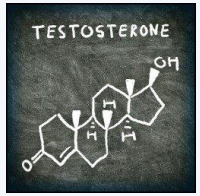
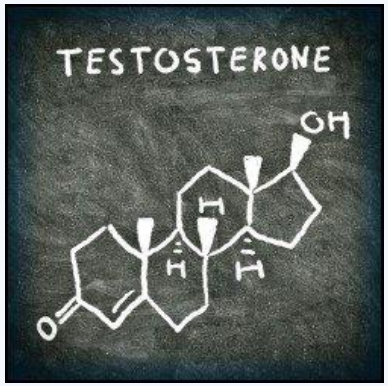
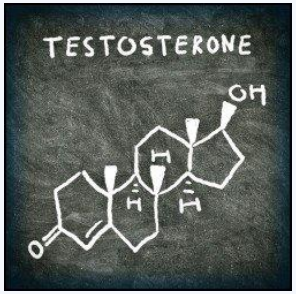


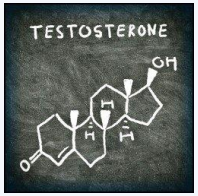




Testosterone Deficiency







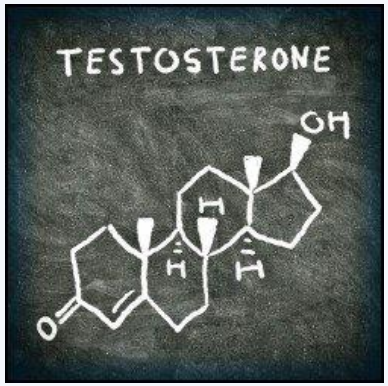
Definition

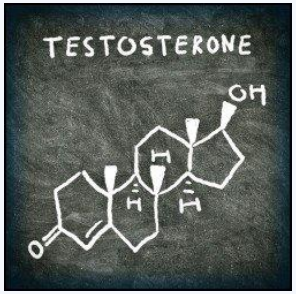
International Society for Sexual Medicine

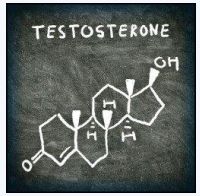
*"Testosterone deficiency (TD) is a **clinical** and **biochemical** syndrome characterized by a deficiency of testosterone, or testosterone action,*

AND

relevant symptoms and signs"



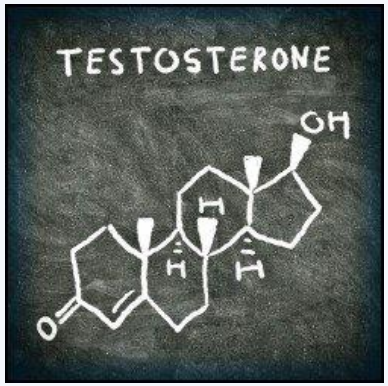


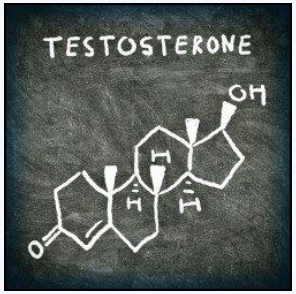


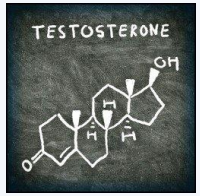
Definition

International Society for Sexual Medicine

*".. may affect the function of **multiple** organ systems, and result in significant detriment in quality of life, including alterations in sexual function."*







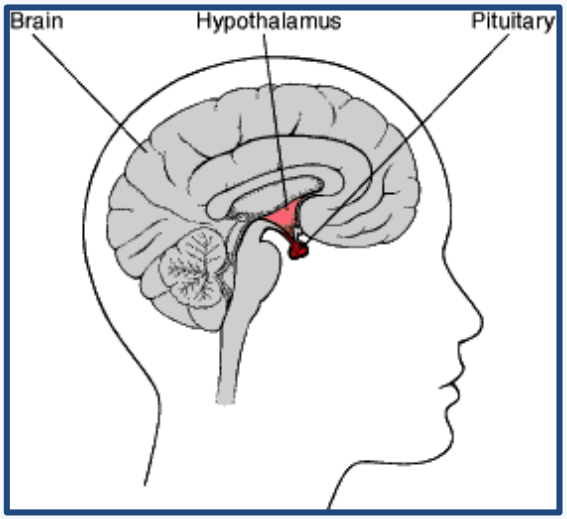
Types of T deficiency

Primary:

- **Testicular** problem leading to ↓ synthesis
- ↑ LH levels

- Various testicular causes
- Seen with ↑ age (mixed picture)

Types of T deficiency



Secondary:

- ↓ LH to stimulate Leydig cells
- *More common* than primary

- Seen with ***obesity*** and ***type 2 DM***
- Opioids, steroids, other medications
- Also with ↑ age (mixed picture)

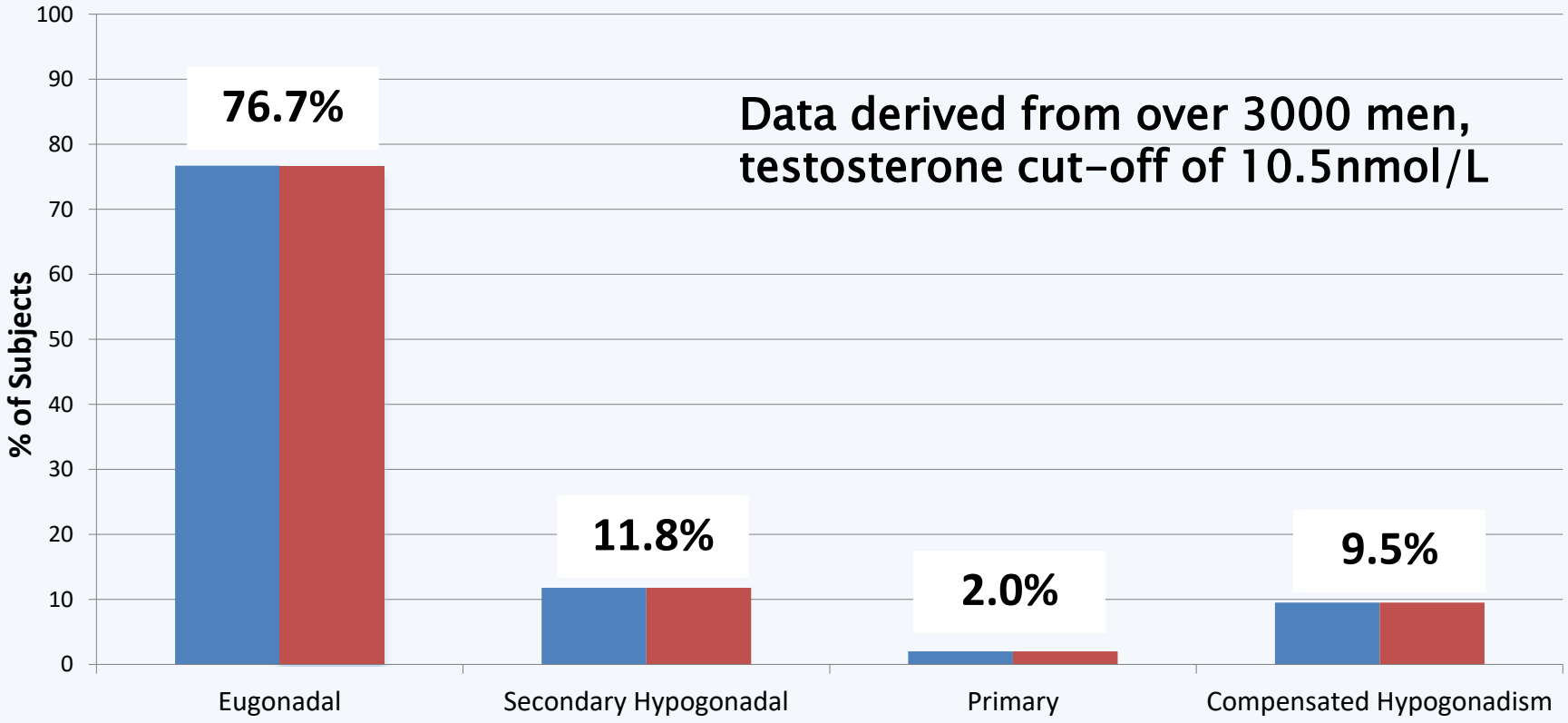
Epidemiology of TD

- Estimates for prevalence vary
- Ranges from 2-12% of men over 40 / 50
- Increases with age

Tajar A, Forti G, O'Neill TW et al. J Clin Endocrinol Metab. 2010;95:1810-8.
Araujo AB, O'Donnell AB, Brambilla DJ, et al. J Clin Endocrinol Metab. 2004;89:5920-5926

European Male Aging Study

Distribution and Selected Characteristics of Men Ages 40–70 (Tajar et al, 2010)



Tajar A, Forti G, O'Neill TW et al. J Clin Endocrinol Metab. 2010;95:1810-8.

Associated conditions

Andrologic and endocrinologic	Metabolic diseases associated with insulin resistance	Cardiovascular diseases	Other chronic diseases	Pharmacologic
Delayed puberty	Obesity	Hypertension	Chronic obstructive pulmonary disease	Oral glucocorticoid treatment
Cryptorchidism	Metabolic syndrome	Coronary artery disease	Obstructive sleep apnea	Regular opioid use
Pituitary disease	Type 2 diabetes	Cerebrovascular disease	End-stage renal disease	Antipsychotic medications
Infertility		Chronic heart failure	Cirrhosis	Androgen deprivation therapy
Varicocele		Atrial fibrillation	Osteoporosis	Methadone maintenance therapy
			Rheumatoid arthritis	Antiretroviral therapy
			HIV	Chemotherapy + radiation
			cancer	Anticonvulsant therapy

Adapted from Hackett et al (2017),1 Dohle et al (2017)4 and Khera et al (2016)

Hackett G et al. BSSM guidelines on adult testosterone deficiency: J Sex Med. 2017 ;14(12):1504-1523.
Khera M et al. J Sex Med 2016;13:1787-1804.

Prevalence Rates and Odds Ratios for Selected Co-Morbidities in Untreated Men ≥ 45 Years

Medical Condition	Hypogonadism Prevalence Rate (95% C.I.)	Odds Ratio (95% C.I.)
Obesity	52.4 (47.9 – 56.9)	2.38 (1.93 - 2.93)
Diabetes	50.0 (45.4 – 54.5)	2.09 (1.70 - 2.58)

Mulligan T et al. Int J Clin Pract 60: 762-769 (2006

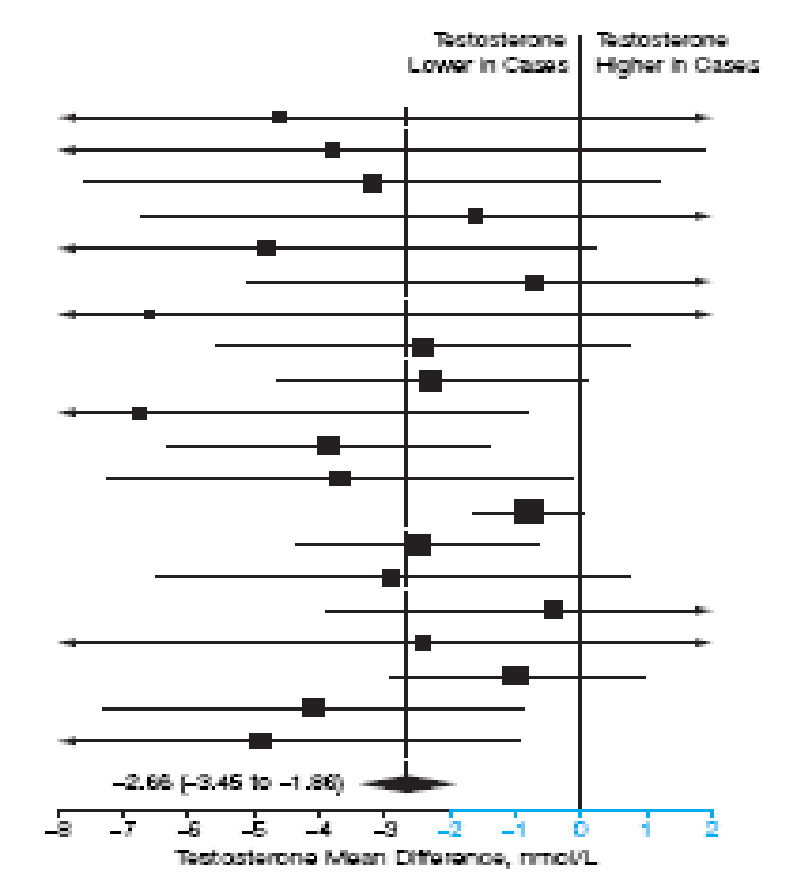
Screening for TD

Recommendations—screening	LoE	Grade
Screen for TD in adult men with consistent and multiple signs of TD	3	C
Screen all men presenting with ED, loss of spontaneous erections, or low sexual desire	1	A
Screen for TD in all men with T2DM, BMI > 30 kg/m^2 or waist circumference > 102 cm	2	A
Screen for TD in all men on long-term opiate, antipsychotic, or anticonvulsant medication	2	B

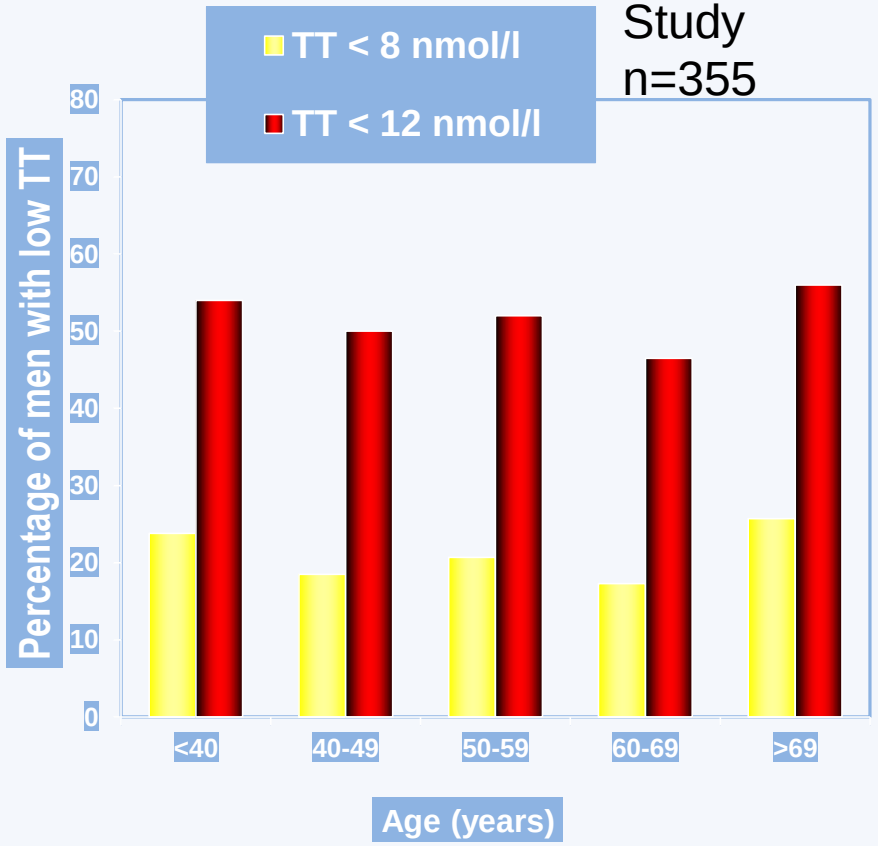
Hackett G et al. BSSM guidelines on adult testosterone deficiency: J Sex Med. 2017 ;14(12):1504-1523
AACE and ACE also advocate screening for TD.Garvey et al 2016

Total Testosterone in men with Type 2 Diabetes

Meta-analysis
20 studies 1982-2005



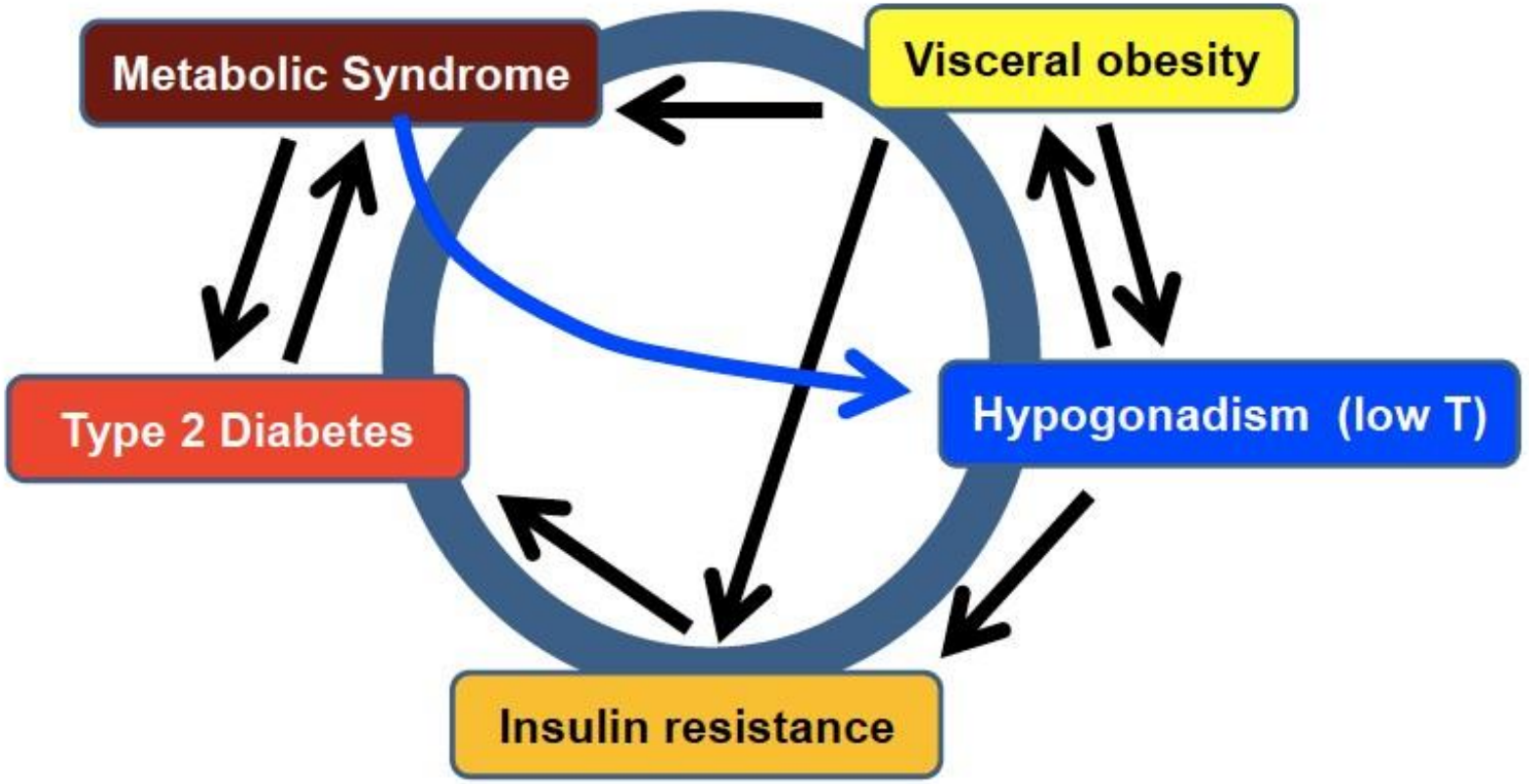
Barnsley Study
n=355



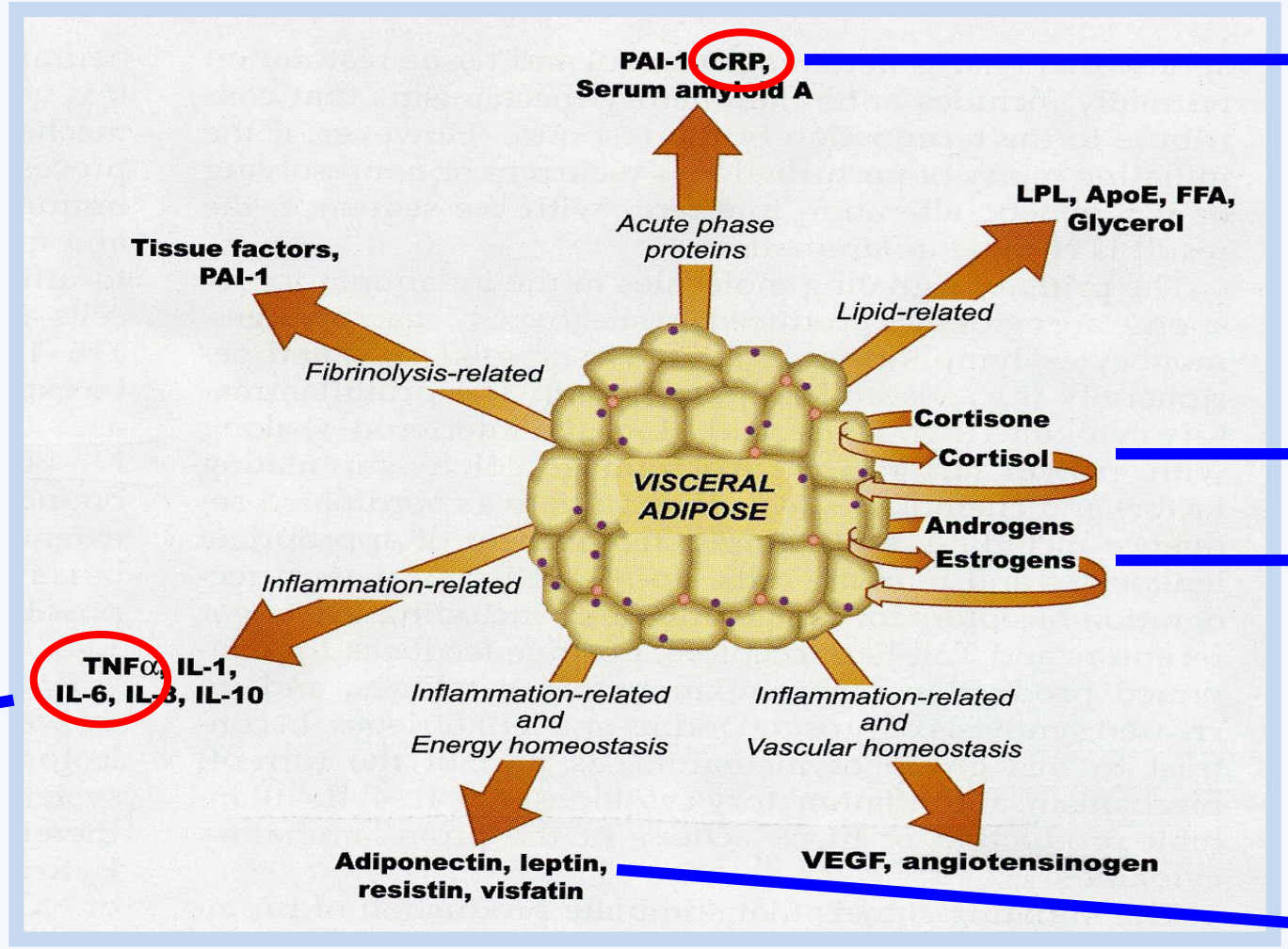
Ding L et al. JAMA 295:1288-1299

Kapoor D et al. Diabetes Care 30: 911–917 (2007)

Low baseline T
→ increased risk to develop Metabolic Syndrome

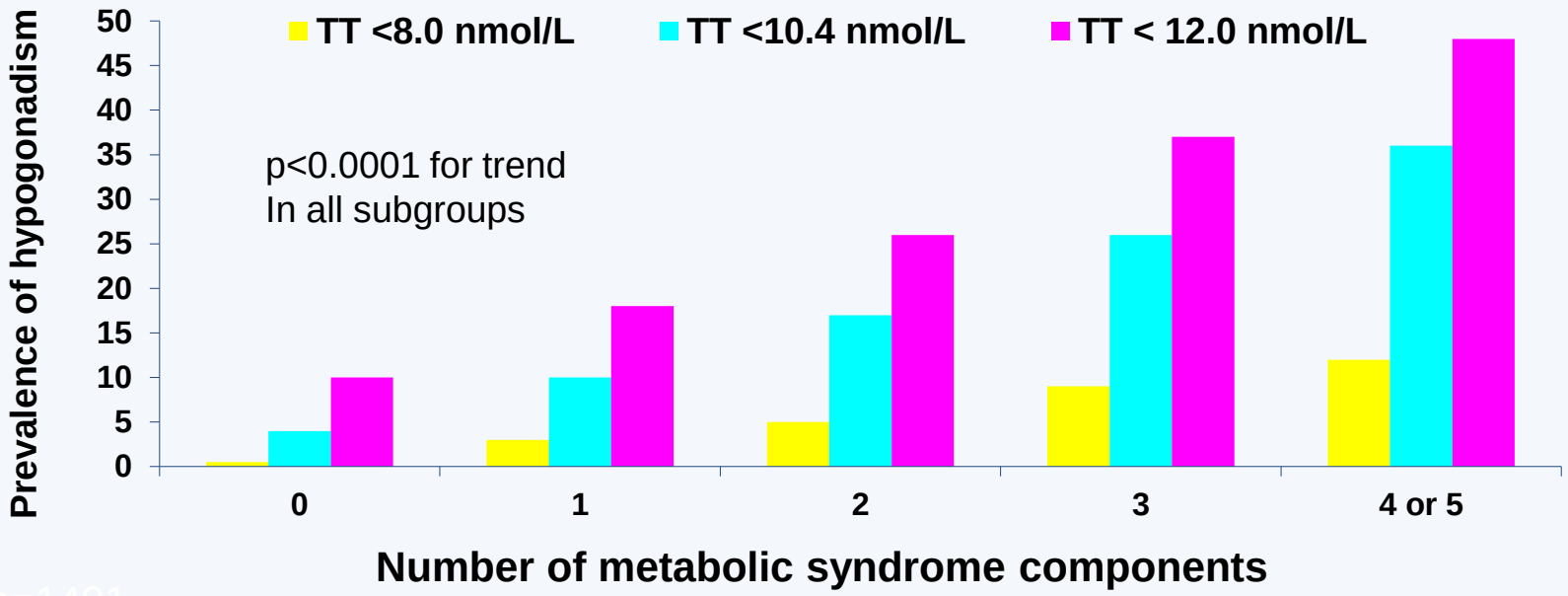


Visceral Fat: An Active Organ



Lyon CJ et al. Endocrinol 144: 2195–2200 (2003), Trayhurn P et al. Br J Nutr 92: 347–355 (2004),
Eckel RH et al. Lancet 365: 1415–1428 (2005)

Testosterone levels associated with number of metabolic syndrome components



n=1491

Corona G et al. Int J Androl 2009]

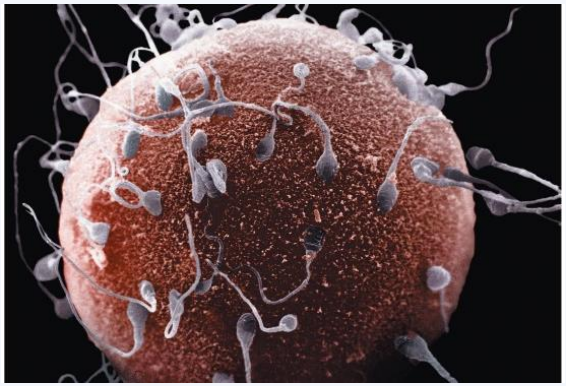
Signs and symptoms suggestive of TD

- Sexual dysfunction symptoms prominent
- Also:
  - night sweats
  - sleep disturbance
  - other changes in mood

Diagnosis of T deficiency

History taking

- Assess **symptoms** (also helps assess response to treatment)
- Other co-morbidities
- Ask re wish to maintain **fertility**
  - *Replacement therapy likely to suppress spermatogenesis & reduce testicular volume*

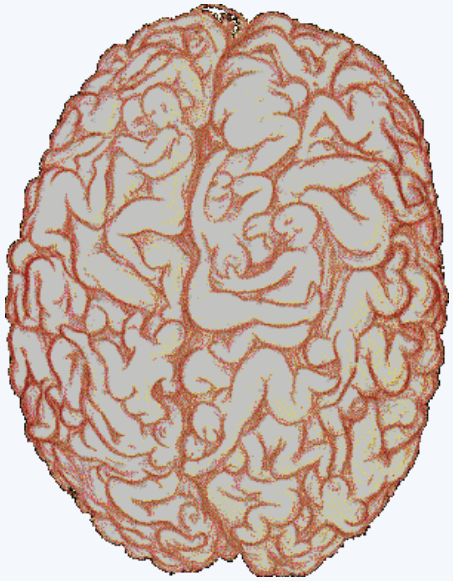


Diagnosis of T deficiency

- Affect:
  - Depression
  - Anxiety
  - Irritability
  - Reduced sense of general well-being
- Cognitive function:
  - Impaired concentration
  - Impaired verbal memory
  - Impaired visual-spatial awareness

Diagnosis of T deficiency

- Physical function:
  - ↓ muscle strength
  - ↓ physical co-ordination
  - ↓ balance
- Sexual function:
  - ↓ sexual desire
  - ↓ nocturnal erections
  - ↓ erectile function
  - ↓ ejaculatory & orgasmic function



ADAM Questionnaire

Your answers to the following questionnaire will help to identify whether you have the features of Testosterone Deficiency Syndrome (TDS).

Please answer the questions honestly.

	YES	NO
1. Do you have a decrease in libido (sex drive)?	☐	☐
2. Do you have a lack of energy?	☐	☐
3. Do you have a decrease in strength and/or endurance?	☐	☐
4. Have you lost height?	☐	☐
5. Have you noticed a decreased "enjoyment of life"?	☐	☐
6. Are you sad and/or grumpy?	☐	☐
7. Are your erections less strong?	☐	☐
8. Have you noticed a recent deterioration in your ability to play sports?	☐	☐
9. Are you falling asleep after dinner?	☐	☐
10. Has there been a recent deterioration in your work performance?	☐	☐

If the answer is YES to question 1 or 7, or at least three of the other questions:

Further evaluate for symptoms of hypogonadism & consider testing

Lab testing for T deficiency

Measure **testosterone** – fasting sample, before 11am

Need at least 2 results, preferably 4 weeks apart

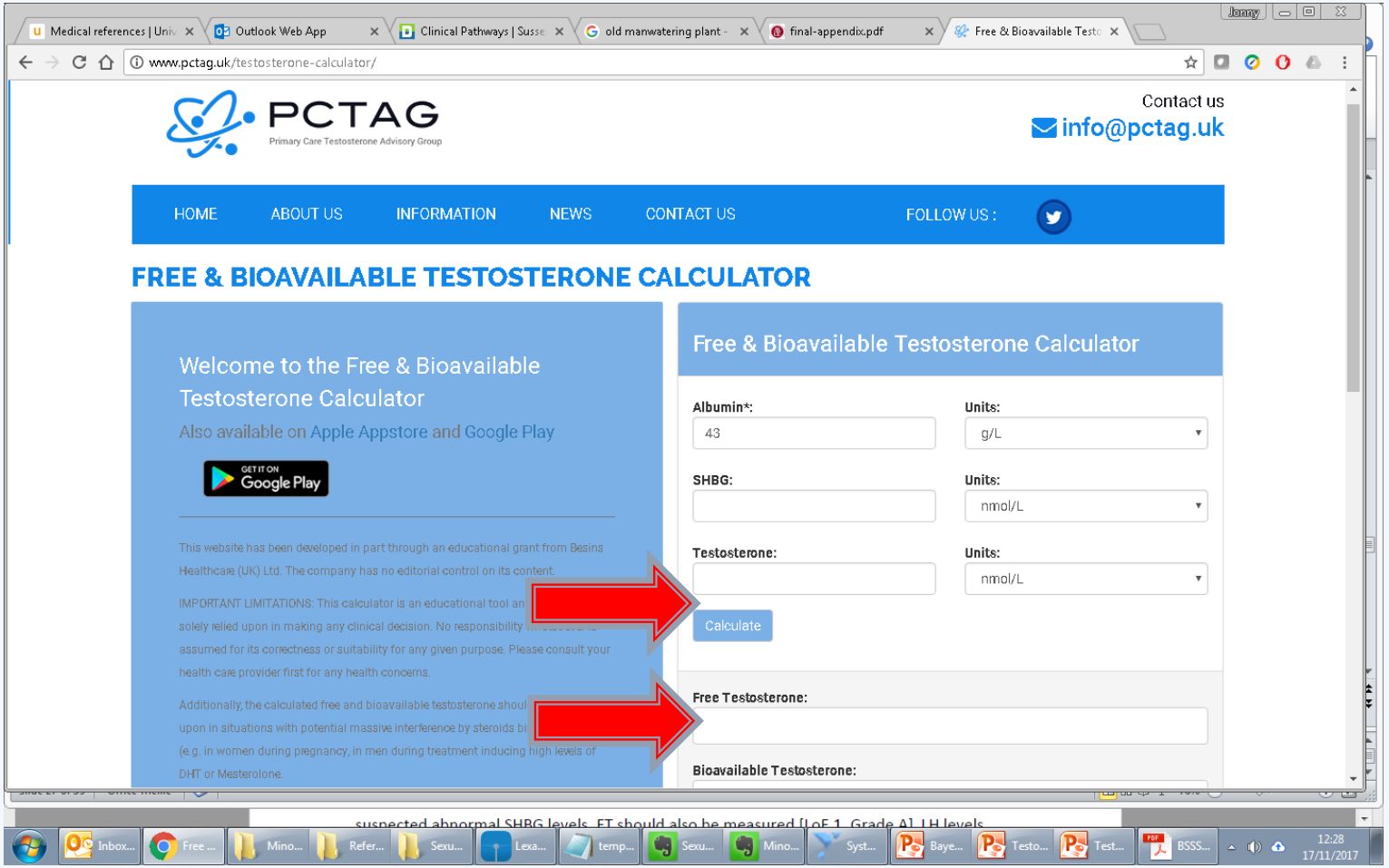
If 1st low/borderline, repeat & measure **LH** +/- FSH, plus **SHBG** to calculate **free** testosterone.

Check **prolactin** if T very low (<5.2nmol/L) & low LH/FSH

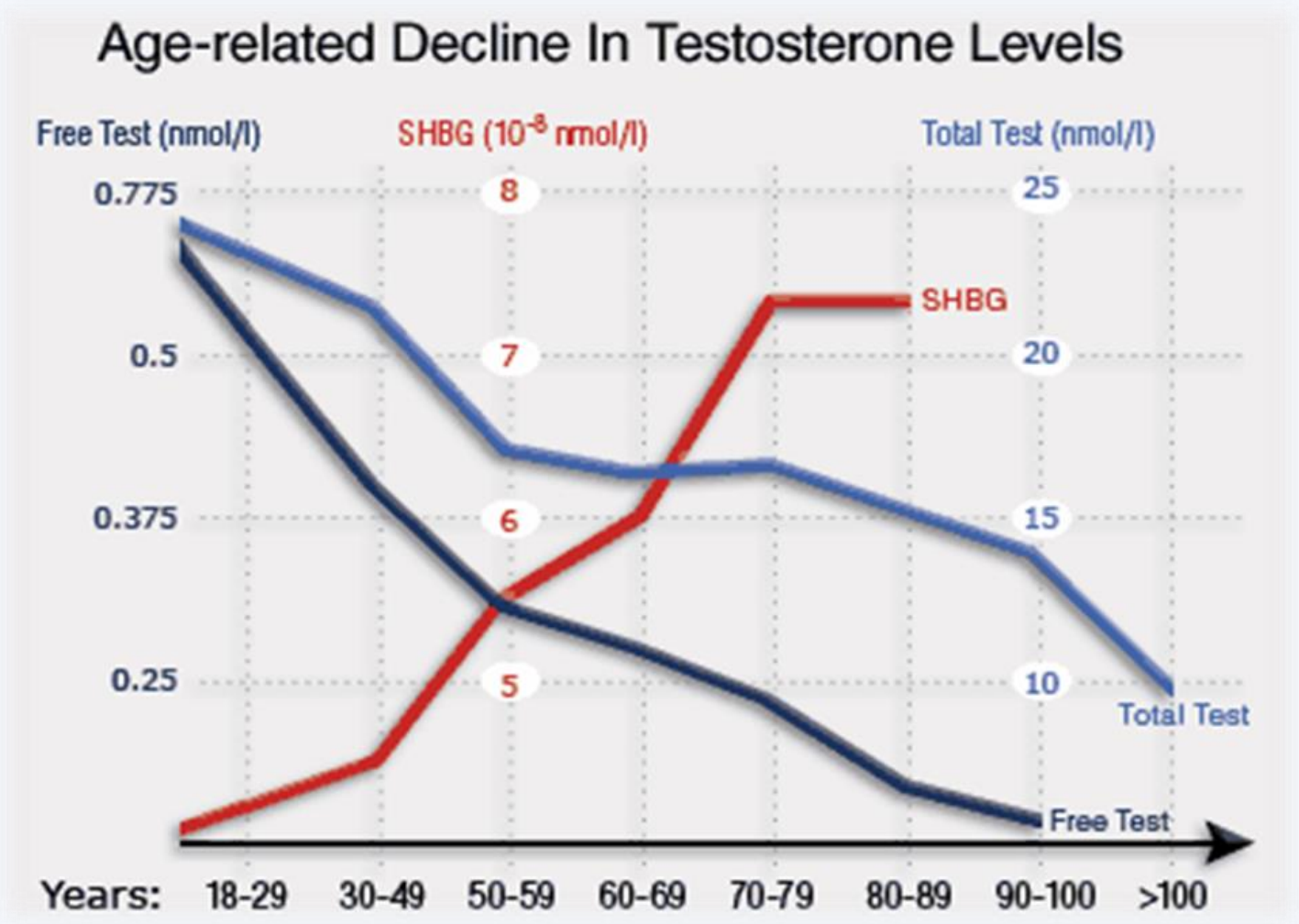
Clinical symptoms more closely related to ***free testosterone*** than total – need the SHBG

Hackett G et al. BSSM guidelines on adult testosterone deficiency: J Sex Med. 2017 ;14(12):1504-1523.

Lab testing for T deficiency



http://www.pctag.uk/



Vermeulen et al ,JCE & M² 1999 , vol 84 ² No 10

Thresholds for diagnosis

- **BEWARE LABORATORY REFERENCES RANGES**
  - Vary considerably across the country
- Use "**Action levels**" instead

Example lab report

Textual Investigations

```
SERUM FREE TESTOSTERONE:
LH, SERUM:
```

Coded Investigations

Serum albumin level (XE2eA)	43 g/L [35 - 52]
Serum testosterone level (XE2dr)	8.7 nmol/L [6.68 - 25.7]
Serum sex hormone binding globulin level (44CD.)	24 nmol/L [19.3 - 76.4]
Serum free testosterone level (XabD9)	200 pmol/L [163 - 473]
Serum LH level (XM0lv)	4.5 iu/L [1.7 - 8.6]
Serum prolactin level (XaELX)	120 mu/L [86 - 324]

Thresholds for diagnosis

- Total T level <8 nmol/L *or* free T <180 pmol/L
  - Usually requires T Therapy
- Total T level >12 nmol/L *or* free T >225 pmol/L
  - Does not require T Therapy
- Total T 8–12 nmol/L *or* free T 180–225 pmol/L
  - May require a ***trial*** of T Therapy, minimum of 6 months

Hackett G et al. BSSM guidelines on adult testosterone deficiency: J Sex Med. 2017 ;14(12):1504-1523.

Treatment of T deficiency

1) Lifestyle measures first
   - Weight reduction
   - Lifestyle modification
   - Optimal management of co-morbidities
2) BUT:
   - **Weight loss alone** does not give the symptomatic benefit seen with **adding testosterone therapy**

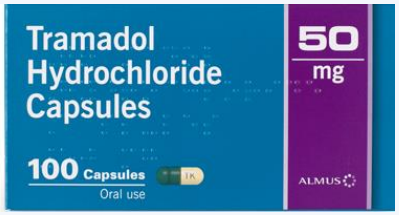
3) THEREFORE:
   - Guidance advises ***combination of both***

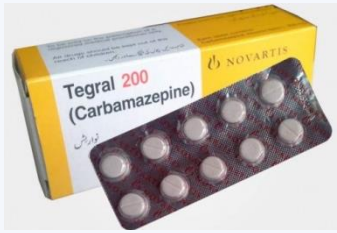
1) Ng Tang Fui M, et al. Int J Obes 2017;41:420-426. 2) Ng Tang Fui M et al. BMC Medicine 2016;14:153.
3/Hackett G et al. BSSM guidelines on adult testosterone deficiency: J Sex Med. 2017 ;14(12):1504-1523.

Treatment of T deficiency

Medication review:

- Swap or stop medications if could be contributing





Testosterone Therapy (TT)

- Choice usually = **gel** vs **injection**
- No justification for selecting one over another except **patient choice**

Hackett G et al. BSSM guidelines on adult testosterone deficiency. J Sex Med. 2017 ;14(12):1504-1523.

Testosterone gels

- Daily, may need titrating
- *Advantages*:
  - Fast onset
  - Levels peak at 2–4 hours then gradually ↓
- *Disadvantages*:
  - Skin irritation
  - Potential interpersonal transfer
  - Possible non-compliance long-term

Testosterone injections

1. Short-acting:

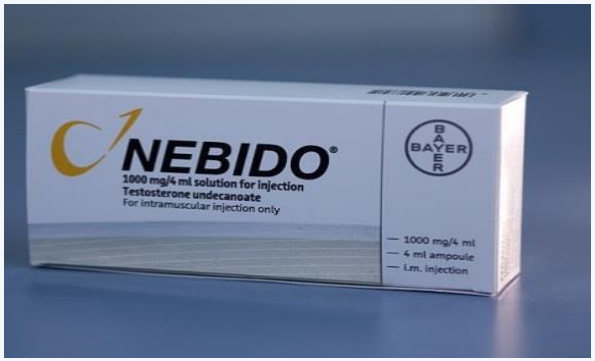
- Usually 3-weekly

- *Advantages*:
  - Low cost prescription (Sustanon)
  - Short duration allows quick withdrawal

- *Disadvantages*:
  - More injections (cost?)
  - Fluctuation in T levels between injections

Testosterone injections

Testosterone Undecanoate



2. Long-acting:

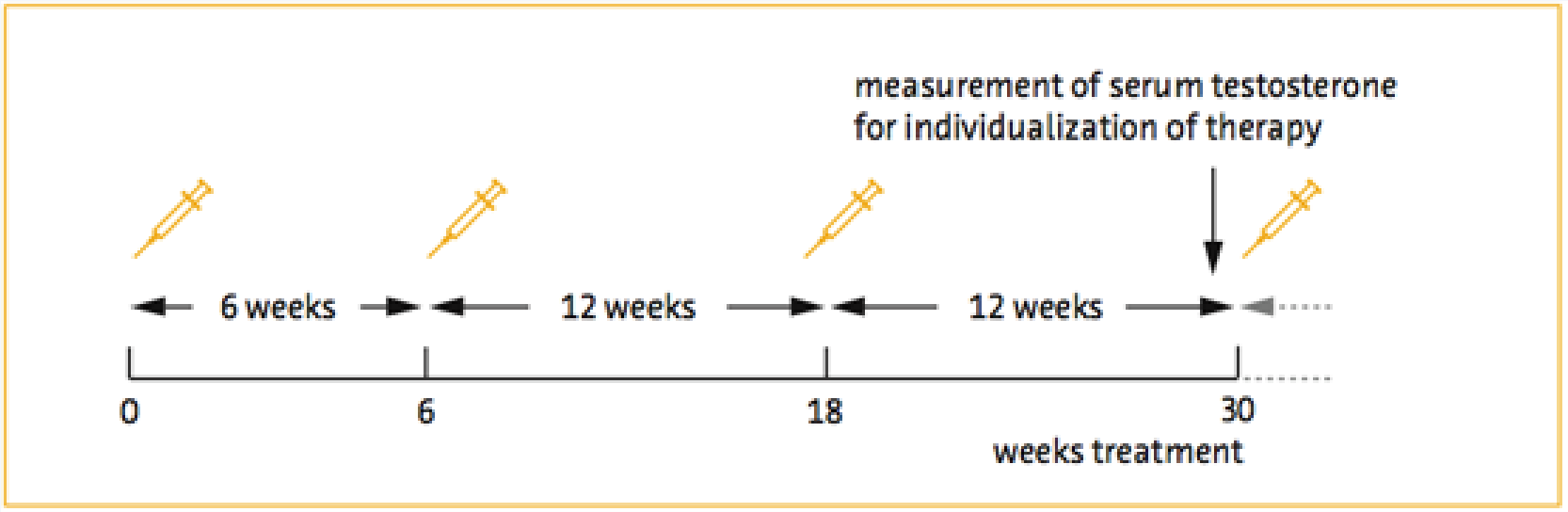
- Every 10-14 weeks

- *Advantages*:
  - Fewer injections - ↑ compliance
  - Maintains better steady state
- *Disadvantages*:
  - Slower drug withdrawal
  - Possible painful injection site (4ml, needs to be SLOW)

Bayer PLC. Important safety information, guidance on the administration of Nebido (testosterone undecanoate). Available from https://www.medicines.org.uk/emc/product/3873/rmms

Testosterone injections

2. Long-acting:



- Aim for trough levels in the lower 1/3 of normal range
- Adjust dosing interval accordingly

Bayer PLC. Important safety information, guidance on the administration of Nebido (testosterone undecanoate). Available from https://www.medicines.org.uk/emc/product/3873/rmms

How long to trial treatment?

- Different symptoms improve at different rates
  - Mental health improvements quite early
  - Sexual desire within 6 weeks, erections maybe longer
  - ↓fat mass, ↑lean mass: may take 12 months or more
- Should trial for **MINIMUM 6 MONTHS**
- Most commonly, **lifelong therapy**
  - Studies: cessation → relapse & reversal of benefits within 6 mths

Hackett G et al. BSSM guidelines on adult testosterone deficiency: J Sex Med. 2017 ;14(12):1504-1523

Contraindications to TT

Main contraindications:

- Locally advanced/metastatic prostate cancer
- Male breast cancer
- Active desire to have children
- Haematocrit >54%
- Severe chronic heart failure (NYHA class IV)
- Past or present liver tumours
- Hypersensitivity to the active substance or any excipients

Hackett G et al. BSSM guidelines on adult testosterone deficiency: J Sex Med. 2017 ;14(12):1504-1523

Bayer PLC. Important safety information, guidance on the administration of Nebido (testosterone undecanoate). Available from https://www.medicines.org.uk/emc/product/3873/rmms

Adverse effects of TT

- Polycythaemia
- Changes in mood, energy & sexual desire
- Acne
- Gynaecomastia
- ***Sustained supraphysiological levels should be avoided***

Hackett G et al. BSSM guidelines on adult testosterone deficiency: J Sex Med. 2017 ;14(12):1504-1523

Follow–up and monitoring

Recommendations – Follow-up	LoE	Grade
Assess the response to therapy at 3, 6 and 12 months, and every 12 months thereafter	4	C
Aim for a target level of total testosterone 15-30 nmol/l to achieve optimal response	4	C
Monitor haematocrit before treatment, at 3-6 months, 12 months and every 12 months thereafter. Decrease dosage, or switch preparation, if haematocrit >0.54. If haematocrit remains elevated, consider stopping and re-introduce at a lower dose.	4	C
Assess prostate health by PSA and DRE before commencing TRT followed by PSA at 3-6 months, 12 months and every 12 months thereafter	4	C
Assess cardiovascular risk before TRT is initiated and monitor cardiovascular risk factors throughout therapy	1b	A

Hackett G et al. BSSM guidelines on adult testosterone deficiency: J Sex Med. 2017 ;14(12):1504-1523

Cardiovascular risk with TT?

- Number of conflicting studies
- Thorough review published 2016:
  - No significant association with CV events[1]
- Registry study, 2016, 23,900 person-months:
  - No evidence of increased CV risk[2]

1. Onasanya O et al. Lancet Diab Endocrinol 2016;4:943–56
2. Maggi M et al. Int J Clin Pract. 2016;70:843-852

Cardiovascular risk with TT?

August 2015 study:

- Retrospective, 83,000 men >50y with **low T**

European Heart Journal Advance Access published August 6, 2015

European Heart Journal
doi:10.1093/eurheartj/ehv346

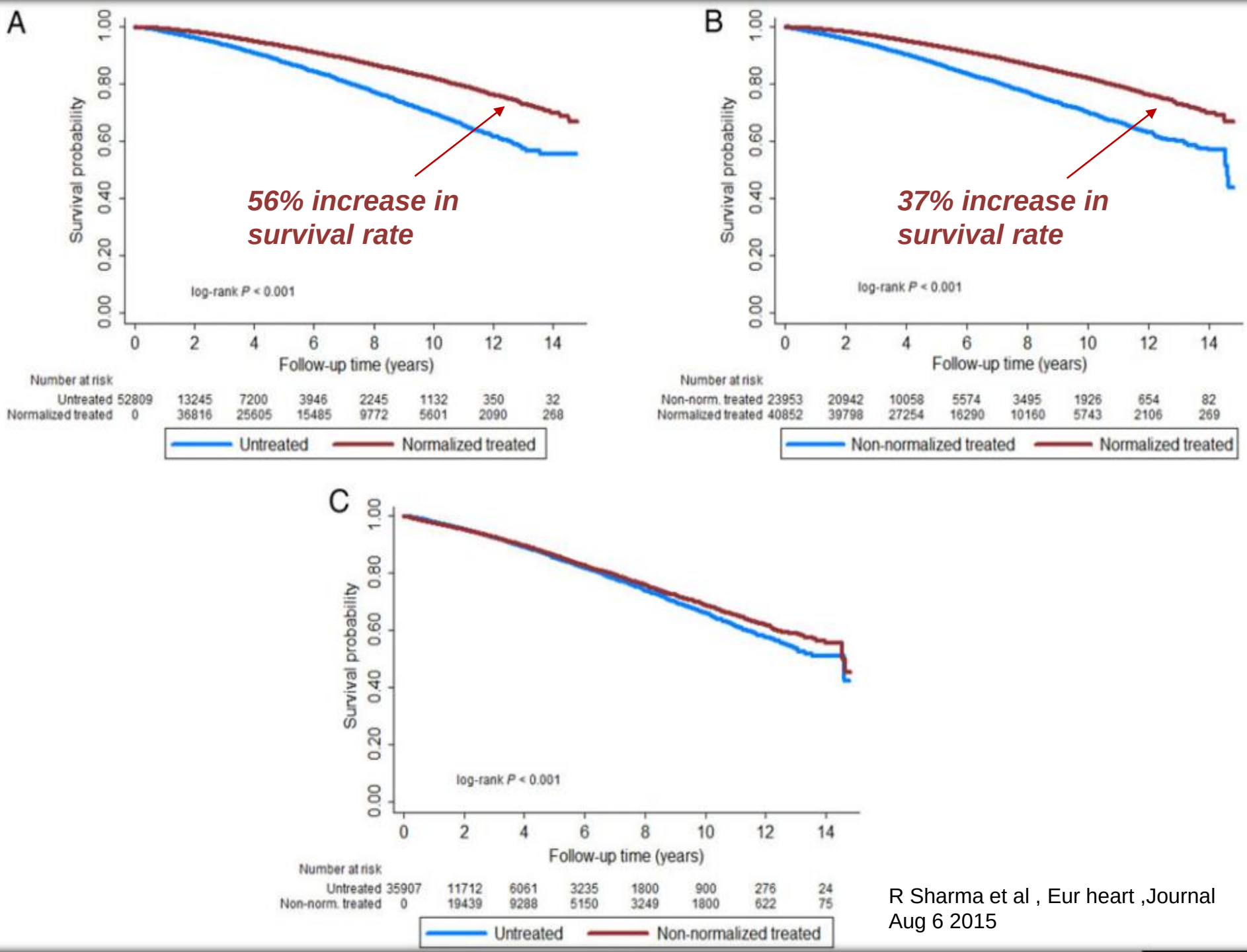
FASTTRACK CLINICAL RESEARCH
Coronary artery disease

Normalization of testosterone level is associated with reduced incidence of myocardial infarction and mortality in men

Rishi Sharma[1], Olurinde A. Oni[1], Kamal Gupta[2], Guoqing Chen[3], Mukut Sharma[1], Buddhadeb Dawn[2], Ram Sharma[1], Deepak Parashara[2,4], Virginia J. Savin[5], John A. Ambrose[6], and Rajat S. Barua[1,2,4]*

[1]Division of Cardiovascular Research, Kansas City VA Medical Center, Kansas City, MO, USA; [2]Division of Cardiovascular Diseases, University of Kansas Medical Center, Kansas City, KS, USA; [3]Division of Health Services Research, University of Kansas Medical Center, Kansas City, KS, USA; [4]Division of Cardiovascular Medicine, Kansas City VA Medical Center, 4801 E. Linwood Boulevard, Kansas City, MO 64128, USA; [5]Division of Nephrology, Kansas City VA Medical Center, Kansas City, MO, USA; and [6]Division of Cardiovascular Medicine, University of California San Francisco, Fresno, CA, USA

Received 2 June 2015; revised 1 July 2015; accepted 6 July 2015



R Sharma et al , Eur heart ,Journal Aug 6 2015

Does It Make A Difference?

Does TT work?

- Good evidence cited in guidelines for improvements in:
  - Sexual desire, activity, erections
  - Waist circumference
  - BMI
  - Lean mass vs fat mass
  - Insulin resistance
  - Lipid profile
  - BP
  - Walking distances
  - Bone mineral density
  - Anaemia
  - Lower urinary tract symptoms
  - Depression scores

Hackett G et al. BSSM guidelines on adult testosterone deficiency: J Sex Med. 2017 ;14(12):1504-1523.

BLAST Study

- T2DM registers from 7 UK practices
- Total T <12nmol/L , or free T < 250pmol/L
- Long-acting testosterone undecanoate 1,000 mg (Nebido):
  - 30 week double-blind randomised vs placebo
  - followed by 52 weeks of open-label use

Hackett G et al. J Sex Med 2014;11:840–856

Outcomes of Therapy (BLAST) (n=199)

	HbA1c (%)	Weight (kg)	BMI Kg/m2	WC (cm)	TC mmol/l	EF (IIEF)	AMS (pts)	HADS-D	GEQ (% imp)
30 weeks	-0.41	-0.7	-0.3	-2.5	-0.25	+3.0	-5.3	-1.01	46
P value	**0.007**	0.13	**0.01**	**0.012**	**0.025**	**0.006**	0.095	0.64	**<0.001**

Hackett G et al. J Sex Med 2014;11:840–856

WC-Waist circumference TC – Total Cholesterol EF –Erectile function

AMS –Aging male study HADS-D -Depression scale

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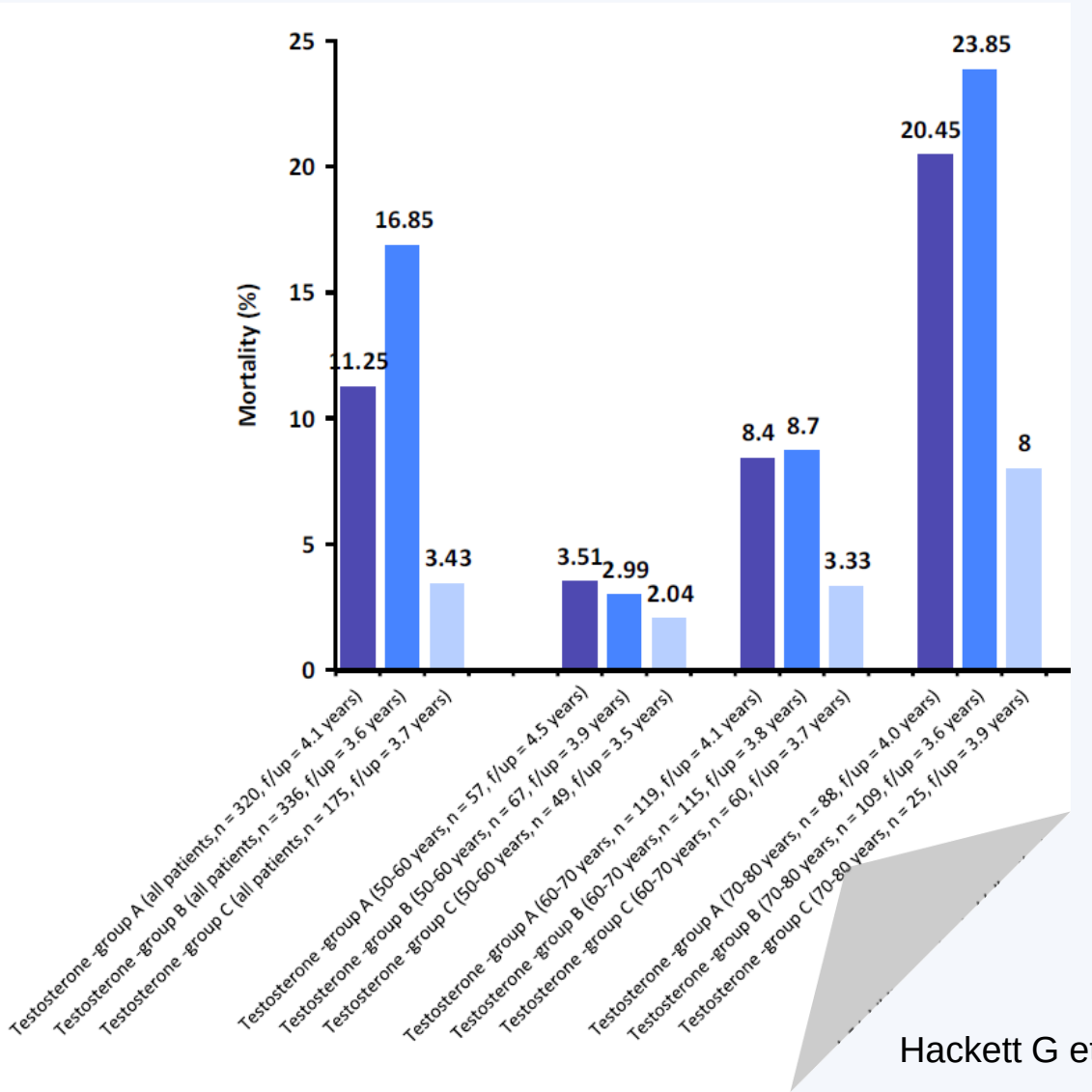
P value	**0.007**	0.13	**0.01**	**0.012**	**0.025**	**0.006**	0.095	0.64	**<0.001**
82 weeks	-0.87	-2.7	-1.00	-4.2	-0.19	+4.31 +9.57 PDE5I	-8.1	-2.18	67-70
P value	**0.009**	**0.016**	**0.019**	**<0.001**	**0.035**	**0.003**	**0.001**	**0.001**	**0.0001**

Hackett G et al. J Sex Med 2014;11:840–856

Serum testosterone, TT and all-cause mortality in men with type 2 diabetes



A. Normal T / untreated

B. Low T / untreated

C. Low T / treated

Hackett G et al. Int J Clin Pract. 2016;70(3):244-53

International Journal of Obesity (2016) **40,** 162–170

www.nature.com/ijo

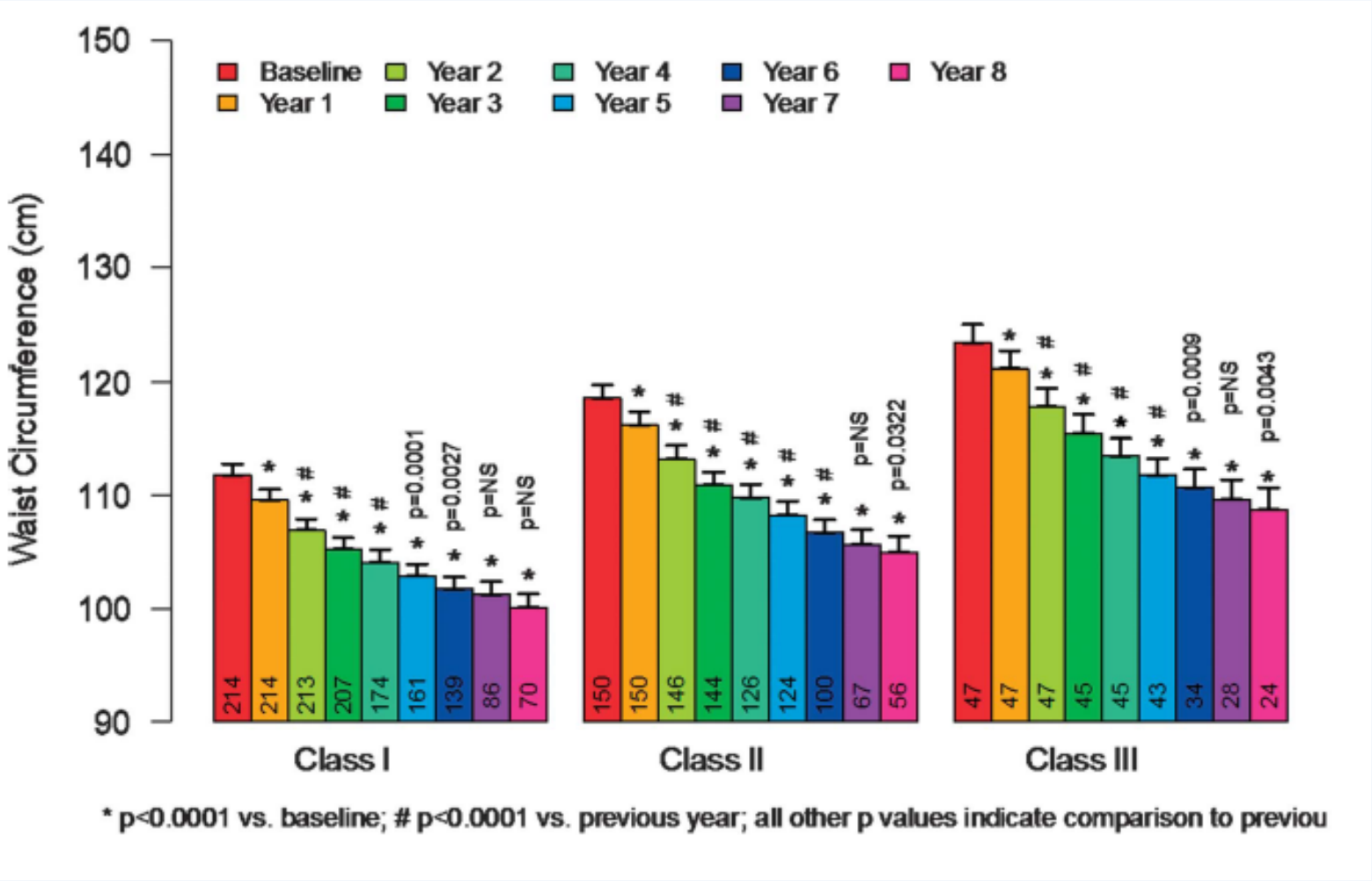
OPEN

ORIGINAL ARTICLE

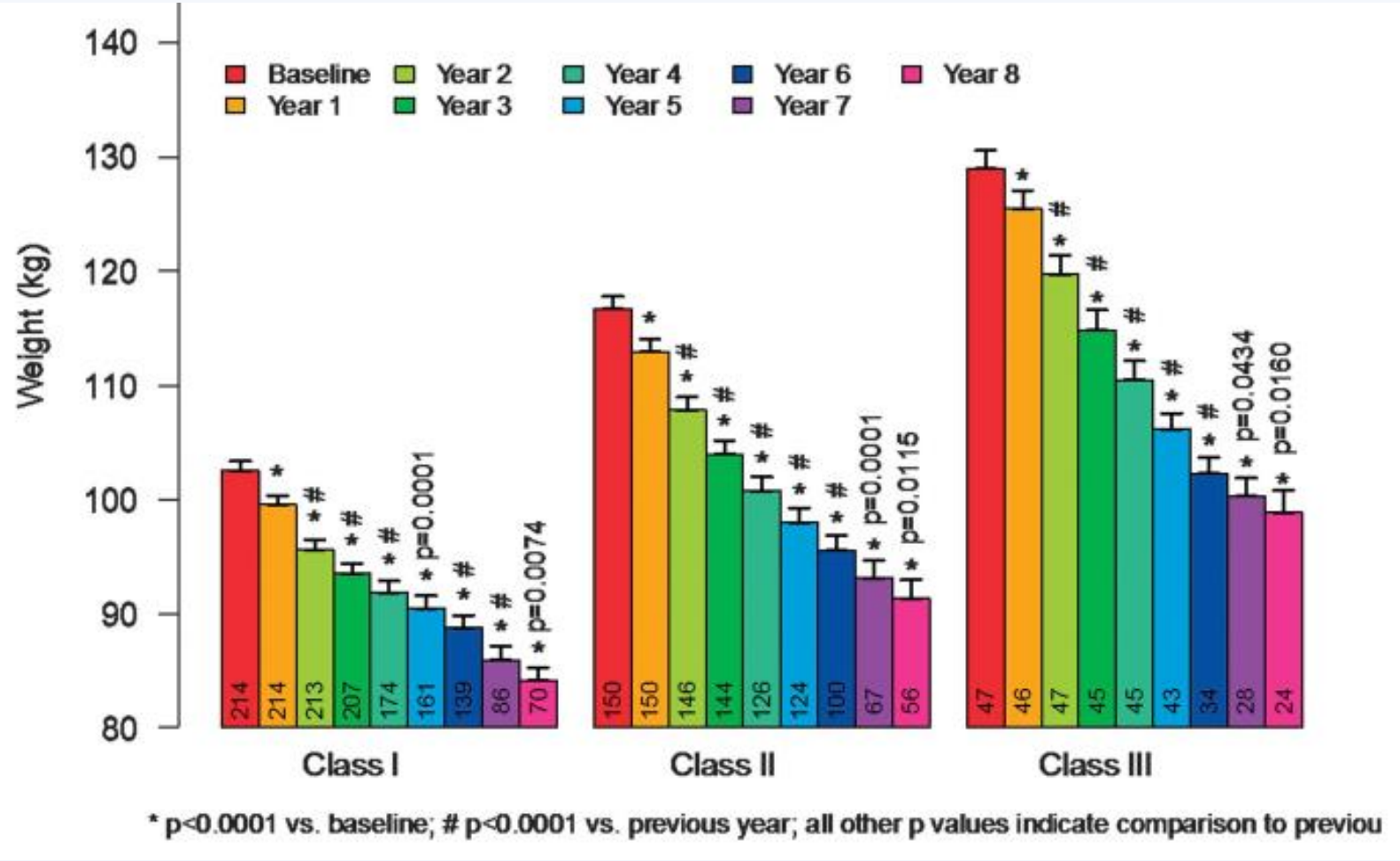
Effects of long-term treatment with testosterone on weight and waist size in 411 hypogonadal men with obesity classes I-III: observational data from two registry studies

F Saad[1,2], A Yassin[2,3,4], G Doros[5] and A Haider[6]

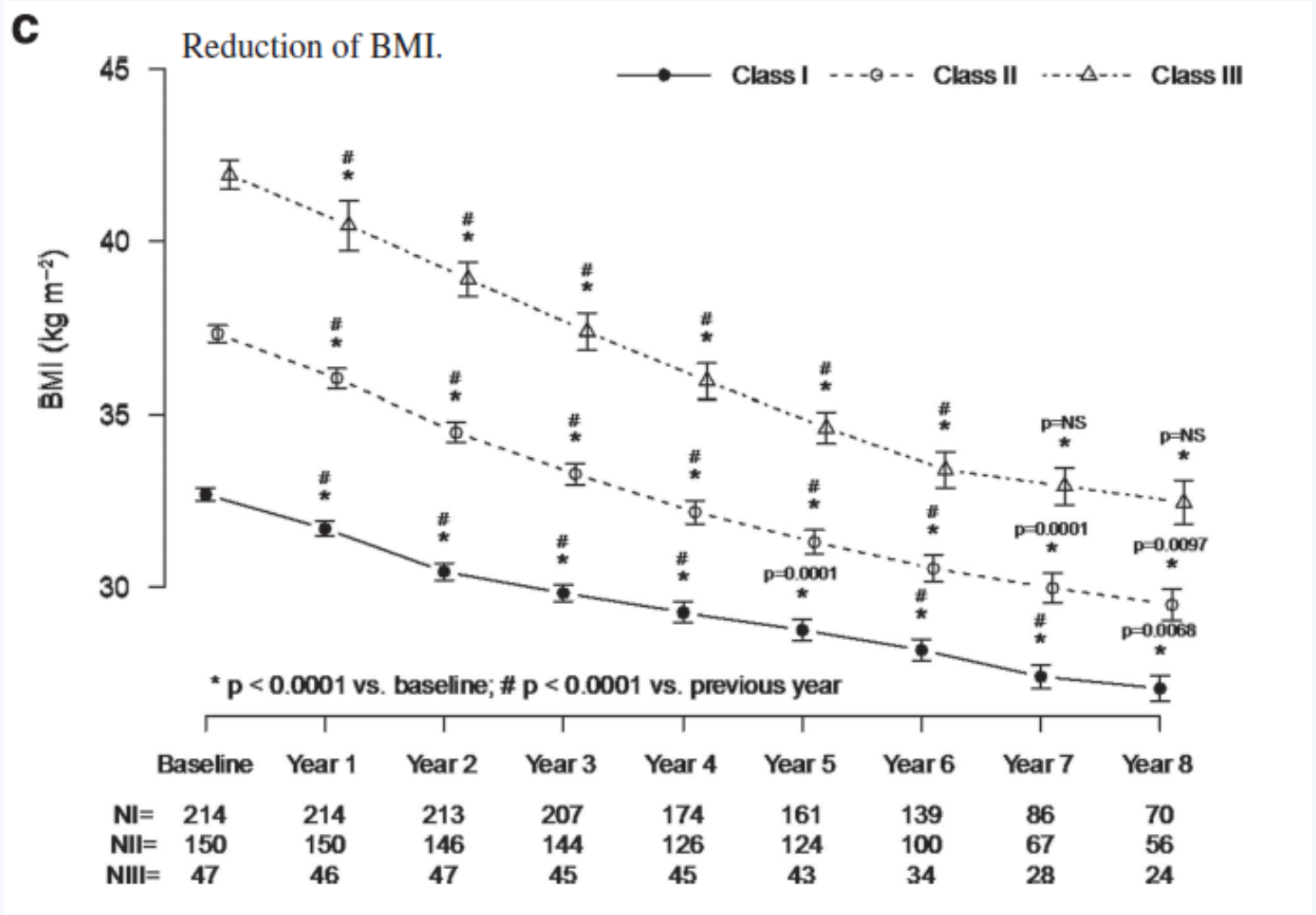
Class I: BMI 30–34.9; n = 214, mean age: 58.61 ± 8.04 years
Class II: BMI 35–39.9; n = 150, mean age: 60.35 ± 5.73 years
Class III: BMI ⩾ 40; n = 47, mean age: 60.51 ± 5.52 years



Saad Et al, Eur J Obesity 2016 Issue 40



Saad Et al, Eur J Obesity 2016 Issue 40



Saad Et al, Eur J Obesity 2016 Issue 40

Resources

THE JOURNAL OF
SEXUAL MEDICINE

British Society for Sexual Medicine Guidelines on Adult Testosterone Deficiency, With Statements for UK Practice

Geoff Hackett, MD,[1] Michael Kirby, MD,[2] David Edwards, MD,[3,*] Thomas Hugh Jones, MD,[4] Kevan Wylie, MD,[5] Nick Ossei-Gerning, MD,[6] Janine David, MD,[7] and Asif Muneer, MD[8,†]

ABSTRACT

Background: Testosterone deficiency (TD) is an increasingly common problem with significant health implications, but its diagnosis and management can be challenging.

Aim: To review the available literature on TD and provide evidence-based statements for UK clinical practice.

Methods: Evidence was derived from Medline, EMBASE, and Cochrane searches on hypogonadism, testosterone (T) therapy, and cardiovascular safety from May 2005 to May 2015. Further searches continued until May 2017.

Outcomes: To provide a guideline on diagnosing and managing TD, with levels of evidence and grades of recommendation, based on a critical review of the literature and consensus of the British Society of Sexual Medicine panel.

Results: 25 statements are provided, relating to 5 key areas: screening, diagnosis, initiating T therapy, benefits and risks of T therapy, and follow-up. 7 statements are supported by level 1, 8 by level 2, 5 by level 3, and 5 by level 4 evidence.

Clinical Implications: To help guide UK practitioners on effectively diagnosing and managing primary and age-related TD.

Strengths and Limitations: A large amount of literature was carefully sourced and reviewed, presenting the best evidence available at the time. However, some statements provided are based on poor-quality evidence. This is a rapidly evolving area of research and recommendations are subject to change. Guidelines can never replace clinical expertise when making treatment decisions for individual patients, but rather help to focus decisions and take personal values and preferences and individual circumstances into account. Many issues remain controversial, but in the meantime, clinicians need to manage patient needs and clinical expectations armed with the best clinical evidence and the multidisciplinary expert opinion available.

Conclusion: Improving the diagnosis and management of TD in adult men should provide somatic, sexual, and psychological benefits and subsequent improvements in quality of life. **Hackett G, Kirby M, Edwards D, et al. British Society for Sexual Medicine Guidelines on Adult Testosterone Deficiency, With Statements for UK Practice. J Sex Med 2017;14:1504–1523.**

Key Words: Hypogonadism; Testosterone Deficiency; Testosterone Therapy; Type 2 Diabetes; Erectile Dysfunction

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[1]Good Hope Hospital, Birmingham, and Aston University Bedfordshire, Luton, Bedfordshire, UK;
[2]Faculty of Health and Human Sciences, University of Hertfordshire and The Prostate Centre, London, UK;
[3]Chipping Norton, Oxfordshire, UK;
[4]Barnsley Hospital, University of Sheffield Medical School, and Royal Hallamshire Hospital, Sheffield, UK;
[5]Neurosciences, University of Sheffield, Sheffield, UK;
[6]Cardiff and Vale NHS Trust and University of South Wales TDS, Cardiff, UK; University of Cape Coast, Cape Coast, Ghana;
[7]European Committee of Sexual Medicine (FECSM), Portway Surgery, Porthcawl, Wales, UK;
[8]NIHR Biomedical Research Centre University College London Hospital and University College London, London, UK
*Past Chairman of the British Society for Sexual Medicine.
†Chairman of British Society for Sexual Medicine.

https://doi.org/10.1016/j.jsxm.2017.10.067

A practical guide on the assessment and management of testosterone deficiency in adult men

Based on the 2017 British Society for Sexual Medicine (BSSM) guidelines on adult testosterone deficiency, with statements for UK practice[1]

Why does it occur?

Testosterone deficiency (TD), also known as hypogonadism, may result from:[2–4]

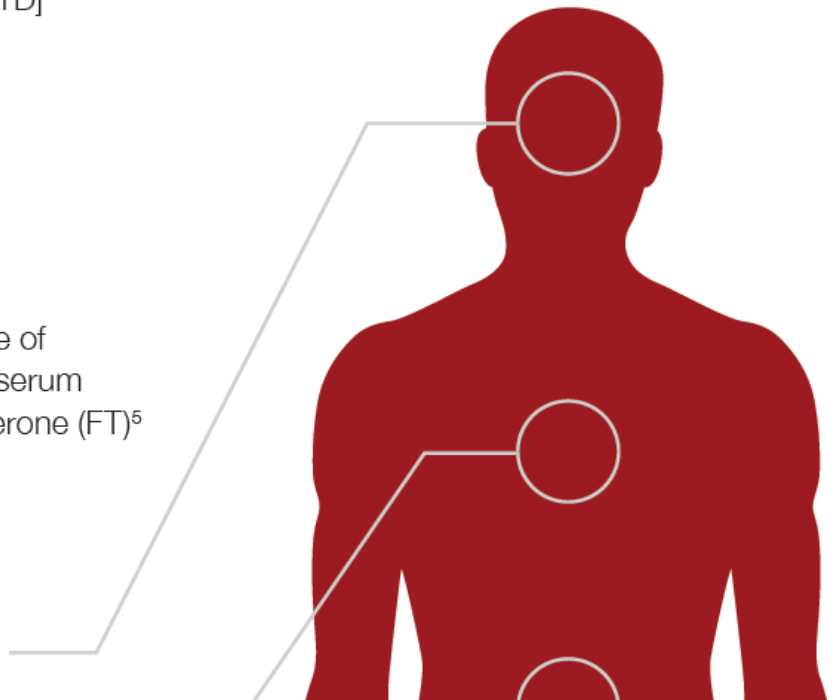
- Problems with the testes [primary (hypergonadotropic) TD]
- Problems with the hypothalamus and pituitary gland [secondary (hypogonadotropic) TD]
- Problems with the hypothalamus/pituitary and testes (combined primary and secondary TD)
- Impaired action/suppression of testosterone

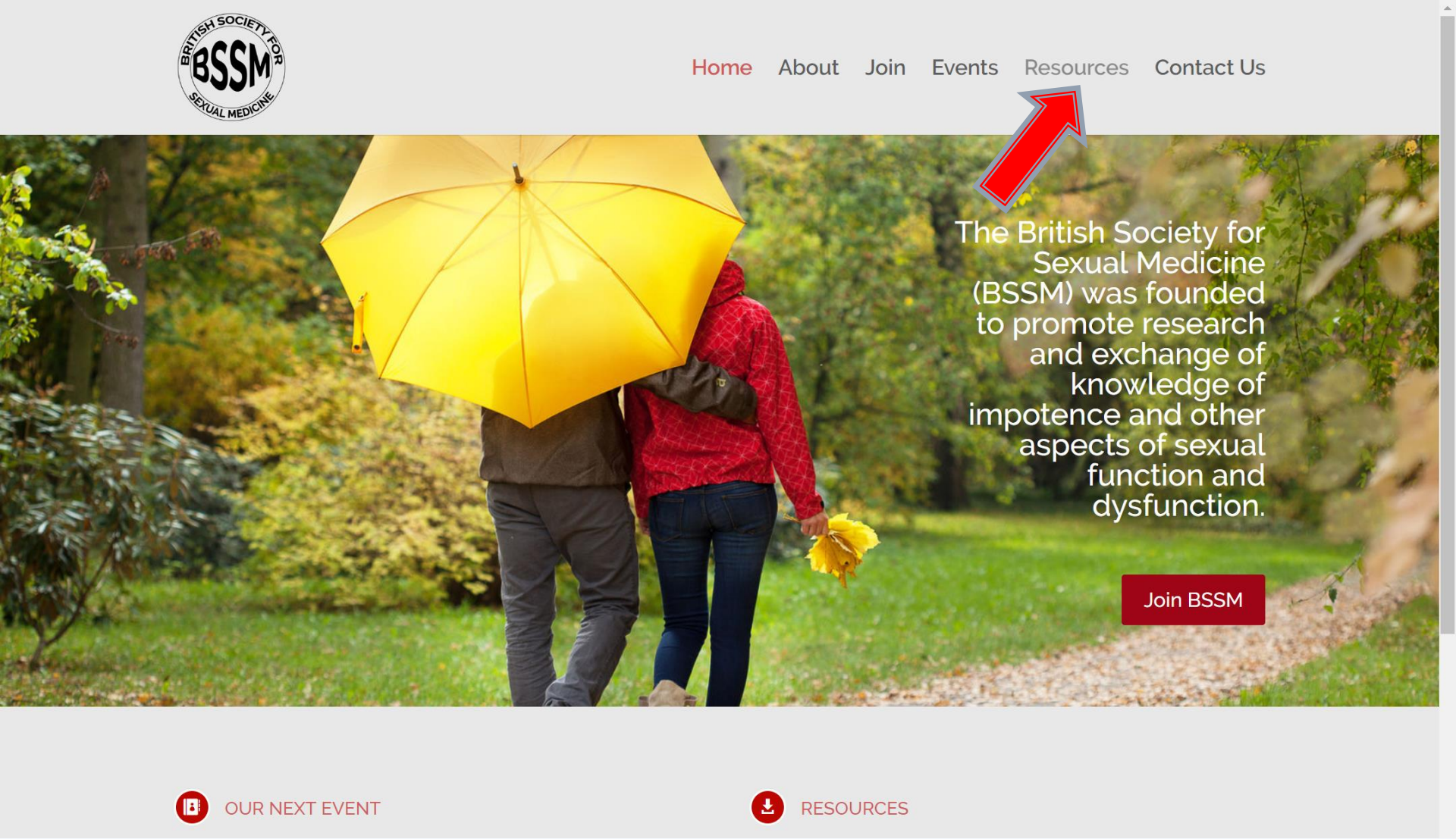
How is it diagnosed?

- The diagnosis of symptomatic TD requires the presence of characteristic signs and symptoms,[2,5–8] PLUS reduced serum concentrations of total testosterone (TT) or free testosterone (FT)[5]

Psychological

- Changes in mood (e.g. anger, irritability, sadness, depression)
- Decreased well-being/poor self-rated health
- Diminished cognitive function (including impaired concentration,

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The British Society for Sexual Medicine (BSSM) was founded to promote research and exchange of knowledge of impotence and other aspects of sexual function and dysfunction.
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A practical guide on the assessment and management of testosterone deficiency in adult men

2018

Guidelines on Adult Testosterone Deficiency, with Statements for UK Practice

A video presentation of these guidelines can be viewed here.

2017

Guidelines on the management of Erectile Dysfunction

2013

Treatment Algorithm for Premature Ejaculation

2013

Management of sexual problems in men: the role of Androgens

2010

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SUPPORTING HEALTHCARE PROFESSIONALS WHO HAVE AN INTEREST IN MEN'S HEALTH ISSUES

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www.bssm.org.uk

www.restoretheman.co.uk

UK POLICY STATEMENTS ON TESTOSTERONE DEFICIENCY[5]

The following statements have been developed following a BSSM Taskforce meeting. The Taskforce examined evidence published between May 2005 to May 2015, containing 1,714 articles, with 52 clinical trials and 32 placebo-controlled randomised controlled trials (RCTs). The following eight key statements were agreed:

1. **Testosterone deficiency is a well-established, significant medical condition.**
2. **Testosterone deficiency has well-established symptoms.**
3. **Testosterone therapy for men with testosterone deficiency is effective, rational, and evidence-based.**
4. **There is no scientific basis for withholding testosterone therapy from men on the basis of age.**

Hackett et al,J Sex Med 2017;14;1504-1523

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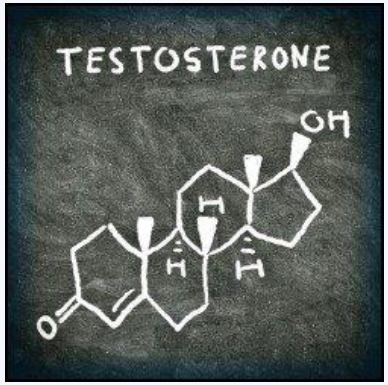
2. **Testosterone deficiency has well-established symptoms.**
3. **Testosterone therapy for men with testosterone deficiency is effective, rational, and evidence-based.**
4. **There is no scientific basis for withholding testosterone therapy from men on the basis of age.**
5. **Testosterone deficiency is associated with increased cardiovascular and all-cause mortality.**
6. **The evidence does not support an increased cardiovascular risk associated with testosterone therapy.**
7. **There is no evidence that supports any increase in the risk of cancer of the prostate with testosterone replacement therapy.**
8. **A major research initiative to explore the benefits of testosterone therapy in cardio-metabolic disease is overdue.**

Hackett et al,J Sex Med 2017;14;1504-1523

Thank you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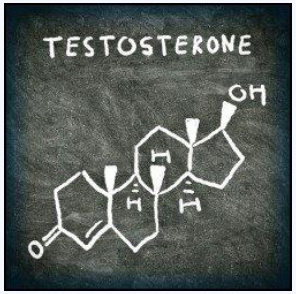
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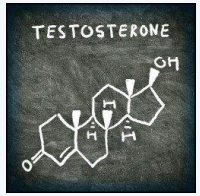
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TESTOSTERONE
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NEBIDO®
Testosterone Undecanoate

Nebido® 1000 mg/4 ml, solution for injection (testosterone undecanoate) Prescribing Information (Refer to full Summary of Product Characteristics (SmPC) before prescribing)

Presentation: 1ml of solution contains 250 mg of testosterone undecanoate, corresponding to 157.9 mg of testosterone. Each 4ml vial of solution contains 1000 mg of testosterone undecanoate. **Indication:** Testosterone replacement therapy for male hypogonadism when testosterone deficiency has been confirmed by clinical features and biochemical tests. **Posology and method of administration:** Strictly for intramuscular use. *Application:* Inject Nebido® extremely slowly. One vial (1000mg) is injected intramuscularly every 10 to 14 weeks. Nebido® should be injected deeply into the gluteal muscle, and must be administered very slowly. Special care should be taken to avoid intravasal injection. The contents of a vial should be injected intramuscularly immediately after opening the vial. *Starting treatment:* Measure serum testosterone levels before the 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 and symptoms regularly; adjust injection interval as appropriate. ***Paediatric population:*** Not for use in children. Not evaluated clinically in males under 18. ***Geriatric patients:*** Based on limited data, no dose adjustment is considered necessary. **Contra-indications:** Androgen-dependent prostate cancer or breast cancer. Past or present liver tumours. Hypersensitivity to testosterone or any of the excipients. Not for use in women. **Warnings and precautions:** Use only if hypogonadism has been demonstrated and if other etiology has been excluded. Limited experience on the safety and efficacy in patients over 65 and no consensus about age specific testosterone reference values. Take into account that physiologically, testosterone serum levels are lower with increasing age 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 testosterone levels at baseline, and at regular intervals during treatment, and adjust individual dosage to ensure maintenance of eugonadal testosterone levels. Periodically check haemoglobin, haematocrit, liver function tests and lipid profile in long-term androgen therapy patients. Androgens may accelerate the progression of sub-clinical prostate cancer and benign prostatic hyperplasia. Use with caution in cancer patients at risk of hypercalcaemia (and associated hypercalciuria), due to bone metastases. Regular monitoring of serum calcium concentration is recommended in these patients. Rarely, liver tumours (both benign and malignant) have been reported. Include liver tumour in differential-diagnostic considerations if severe upper abdominal complaints, liver enlargement or signs of intra-abdominal haemorrhage occur. Efficacy and safety of Nebido® has not been demonstrated in patients with hepatic and renal impairment, therefore testosterone replacement therapy should be used with caution in these patients. Nebido® may cause oedema with or without congestive cardiac failure in patients with severe cardiac, hepatic or renal insufficiency, or in patients with ischaemic heart disease. In this case, stop treatment immediately. Testosterone may cause a rise in blood pressure and Nebido® should be used with caution in men with hypertension. Testosterone and derivatives have been reported to increase the activity of coumarin derived oral anticoagulants. Use with caution in patients with thrombophilia, as thrombotic events during testosterone therapy have been reported in these patients. Use with caution in patients with bleeding disorders, epilepsy, migraine and in patients predisposed to oedema. Improved insulin sensitivity may occur. Irritability, nervousness, weight gain, prolonged or frequent erections may indicate excessive androgen exposure requiring dose adjustment. Pre-existing sleep apnoea may be potentiated. Testosterone may produce a positive reaction in anti-doping tests. Not suitable for developing muscles or increasing fitness in healthy individuals. Withdraw treatment if symptoms of excessive androgen exposure persist or reappear. **Interactions:** Interactions reported with coumarin derived oral anticoagulants (requires dose monitoring), ACTH or corticosteroids, and thyroxin binding globulin in laboratory tests. **Pregnancy and lactation:** Not for use in women. **Effects on ability to drive and use machines:** None known. **Undesirable effects:** Common – injection site pain, acne, polycythaemia, haematocrit increased*, red blood cell count increased*, haemoglobin increased, increased weight, hot flush, increased prostate specific antigen, abnormal prostate examination, benign prostate hyperplasia and various injection site reactions. **Respective frequency has been observed in relation to the use in testosterone containing products.* Serious side effects – *cf. CI/Warnings and Precautions* – in addition, hypersensitivity, cardiovascular disorder, depression, aggression, hypertension, liver function test abnormalities, urinary retention, prostatic intraepithelial neoplasia and prostatitis. Pulmonary microembolism of oily solutions can in rare cases lead to signs and symptoms such as cough, dyspnoea, malaise, hyperhidrosis, chest pain, dizziness, paraesthesia or syncope. These reactions may occur during or immediately after the injection and are reversible. Suspected anaphylactic reactions after Nebido injection have been reported. Other side effects - The following adverse reactions have been reported under treatment with testosterone-containing preparations: nervousness, hostility, sleep apnoea, various skin reactions including seborrhoea, increased frequency of erections, in rare cases, priapism, and, in very rare cases, jaundice. Therapy with high doses of testosterone preparations commonly reversibly interrupts or reduces spermatogenesis, thereby reducing the size of the testicles. Prescribers should consult the SmPC in relation to other side effects. **Overdose:** Reduce dose or terminate therapy. **Incompatibilities:** Must not be mixed with other medicinal products. **Legal Category:** POM. **Package Quantities and Basic NHS Costs:** 1 x 4ml vial (£87.11). **MA Number(s):** PL00010/0549. **Further information available from:** Bayer plc, 400 South Oak Way, Reading, RG2 6AD. Telephone: 0118 2063000. **Date of preparation:** October 2017.

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard. Adverse events should also be reported to Bayer plc. Tel.: 0118 2063500, Fax.: 0118 2063703, Email: pvuk@bayer