

# The Management of Hypogonadism in the Diabetic Patient

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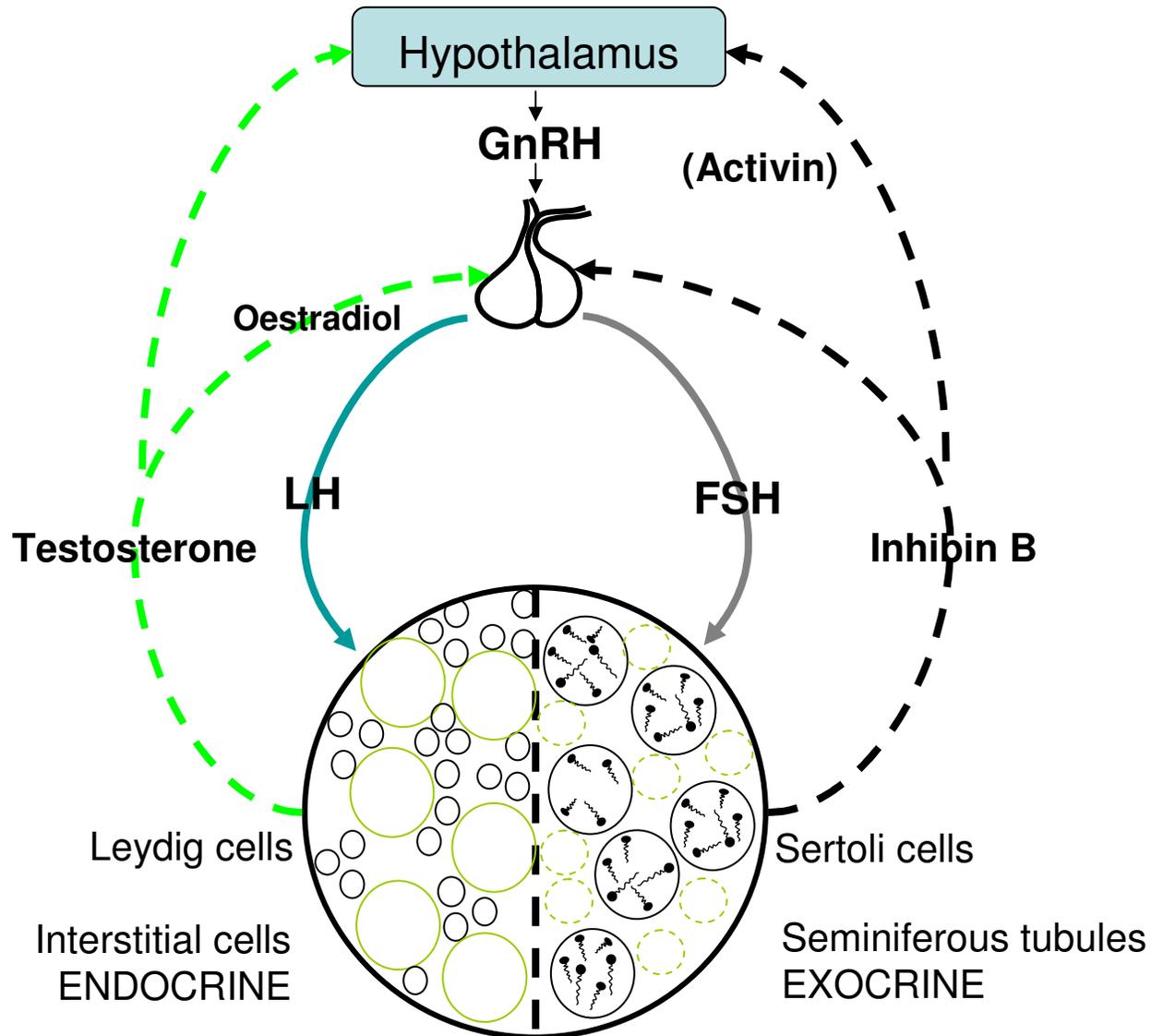
Norfolk & Norwich University Hospital NHS Foundation Trust



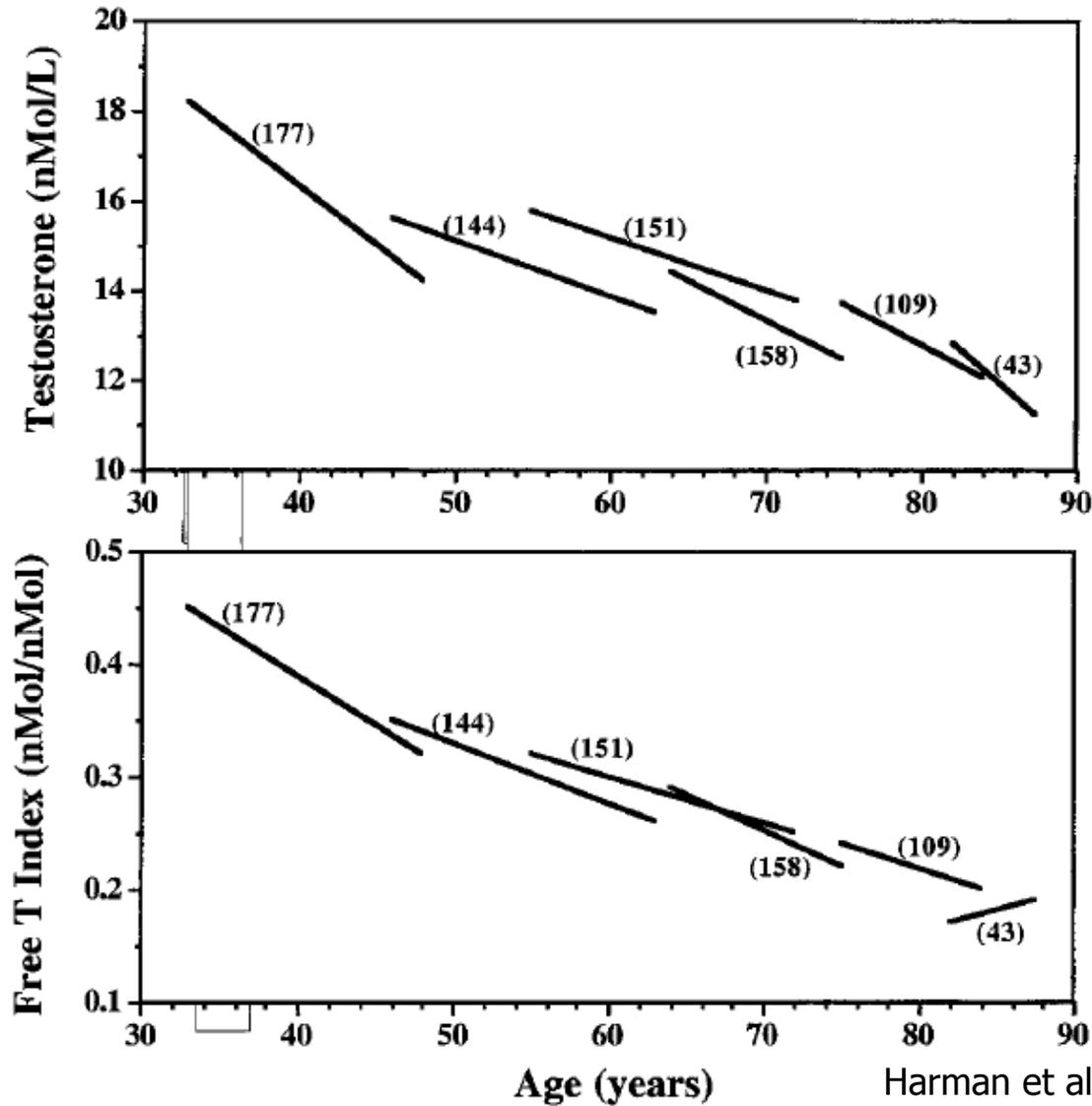
# Definition

- A clinical syndrome of symptoms, with or without physical signs, in conjunction with biochemical evidence of testosterone deficiency
- Most often occurs due to primary testicular failure, or a disruption in the hypothalamic – pituitary – testicular pathway

# Regulation of Testicular Function



# Testosterone Levels Fall With Age



# Late Onset Hypogonadism

- This is a term widely used for testosterone deficiency associated with ageing
- However this term should only be used once other causes of hypogonadism have been excluded

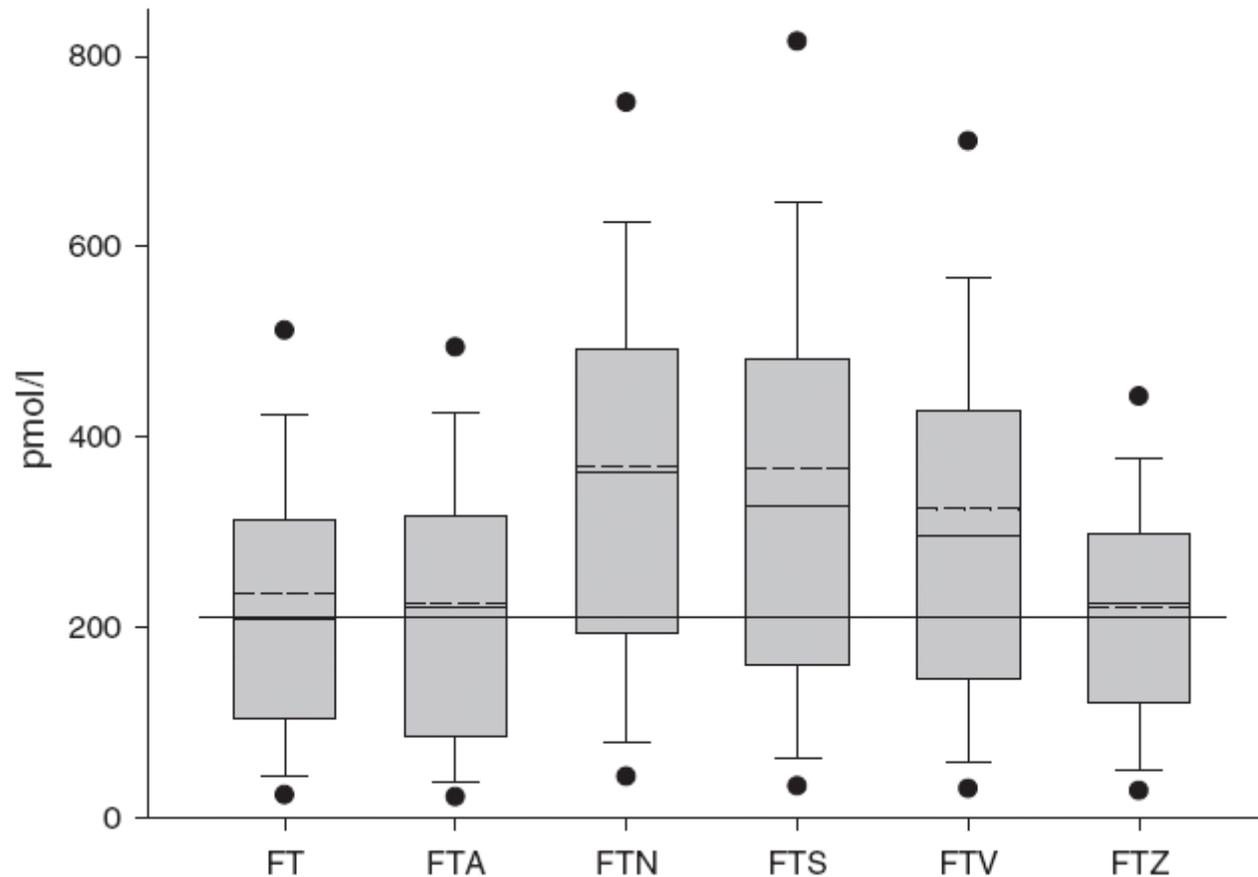
# Diagnosis - Differences of Opinion

- A total serum testosterone (TT) of  $<8$  nmol/l is the recommended definition of hypogonadism by
  - International Society for Andrology
  - ISSAM
  - European Association of Urology
  - European Academy of Andrology
  - American Society of Andrology
- However, the American Endocrine Society suggests it should be  $<10.4$  nmol/L

# Issues to Consider

- That T should be measured between 8 and 11am
- Check the CV of your local assay
- Because evidence suggests that many patients with TT levels between 8 and 12 nmol/L also benefit from TRT and can thus be used for this group of patients

# Measurement Errors



**Comparison of 5 different equations with equilibrium dialysis methods**

Ly et al Clin Endocr 2010;73(3):382-388

# Prevalence

- Depending on the definition, estimates suggest that between a  $\frac{1}{5}$  to a  $\frac{1}{2}$  of all men with T2DM have hypogonadism - but some of these looked only at T levels, not symptoms
- Thus about 20-30% of men with T2DM have both, of whom 30-50% may be assumed to not be eligible for / want TRT
- Thus, about 10-15% of men with T2DM may need TRT

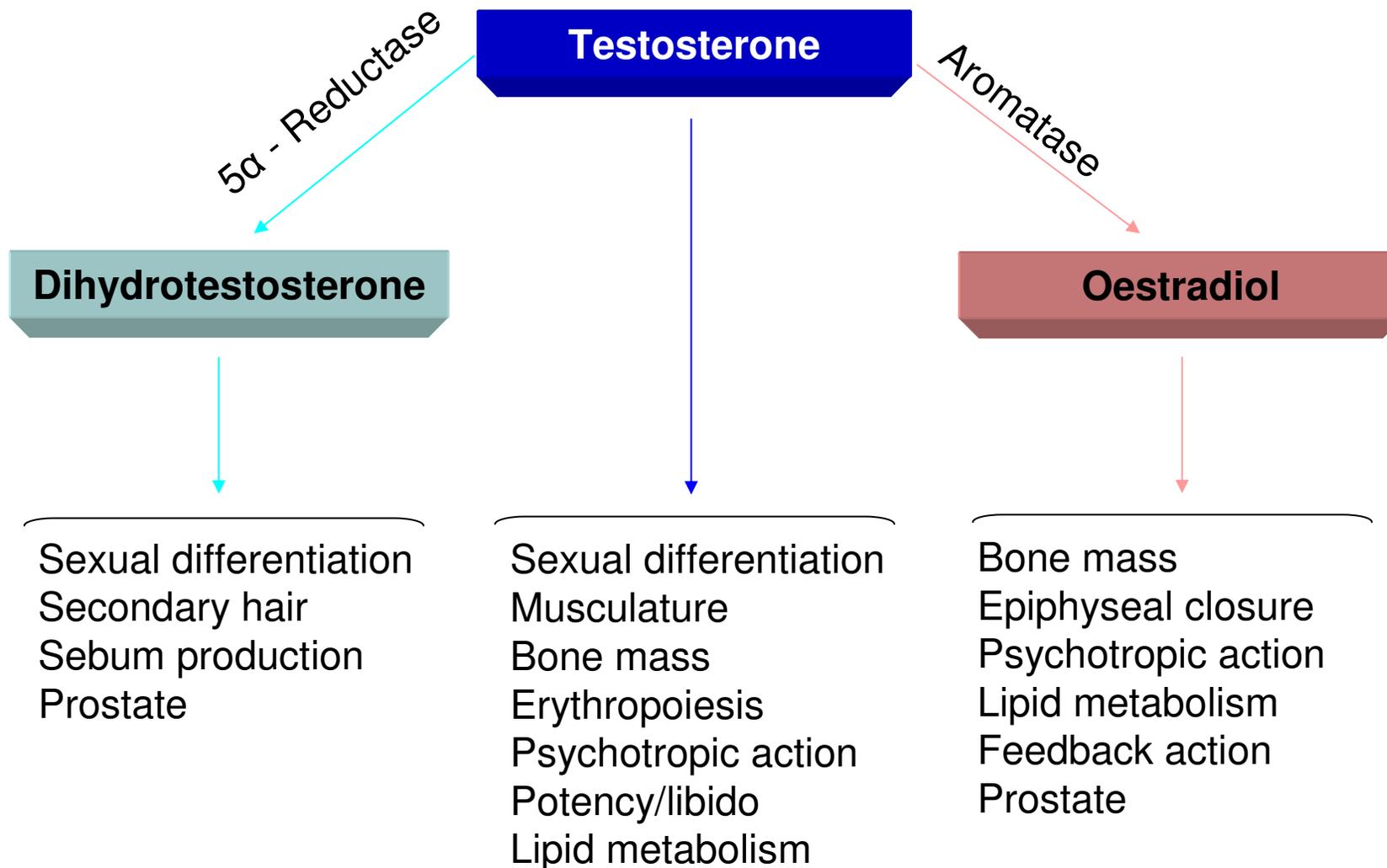
# Obesity and Testosterone

- Low T is associated with insulin resistance and lowered SHBG
- Visceral adipose aromatase consumes testosterone converting it to oestradiol
- Raised oestradiol levels then inhibit the hypothalamic-pituitary-testicular response to further lower testosterone levels

# Symptoms

- Reduced or loss of libido
- Reduced quality and frequency of erections
- Fatigue, reduced physical strength and endurance
- Changes in mood with depressed mood and irritability
- Sleep disturbances
- Reduced motivation
- Hot flushes and sweats
- Change in body composition, with in less lean body mass and increased visceral fat
- Sarcopaenia
- Decreased body hair and skin alterations
- Gynaecomastia
- Subfertility
- Reduced bone mineral density
- Low haematocrit

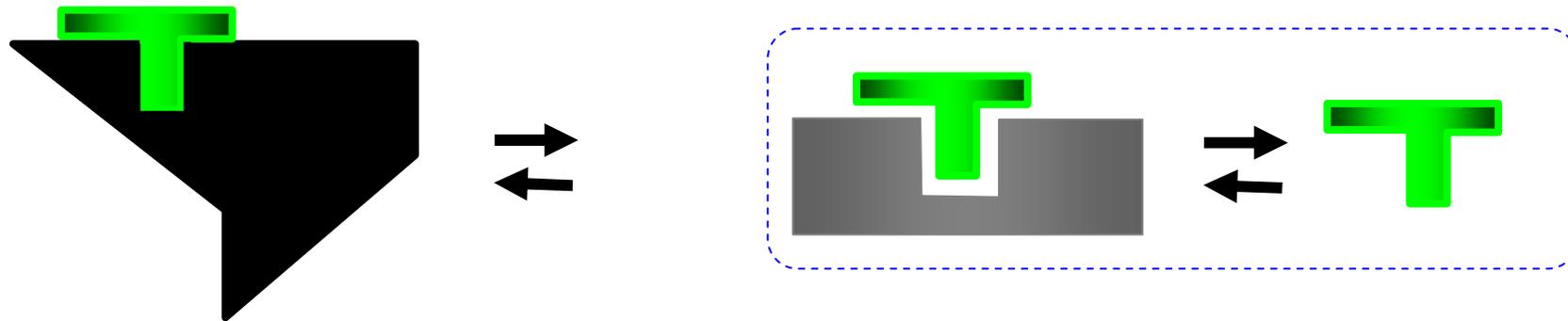
# Testosterone and its Metabolites



# Approach

- Ask for a blood test between 8 am and 11 am
  - If this is above 12 nmol/L then hypogonadism can safely excluded.
  - However, if it is lower than 12 nmol/L then the level should be repeated
  - In addition ask for LH, FSH, SHBG, ferritin, and prolactin
- Don't be caught out by the inappropriately 'normal' LH/FSH in the face of a low T

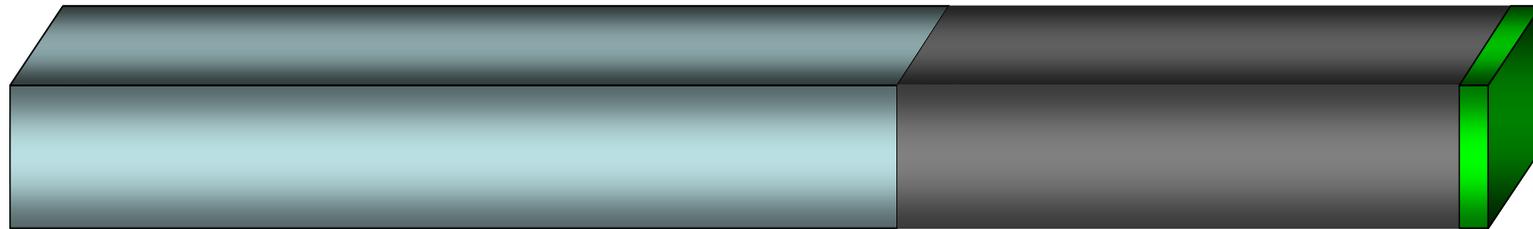
# Binding of Testosterone



T firmly bound  
to SHBG  
**60%**

T loosely bound  
to albumin  
**38%**

Free T  
**2%**



**BIOAVAILABLE TESTOSTERONE**  
= Albumin-bound T + Free T

# Age, Diabetes, SHBG, Testosterone

- A few things to muddy the waters.....
  - Ageing cause a rise in SHBG
  - Obesity and insulin resistance cause a lowering of SHBG
  - The aromatisation of T to oestradiol causes a rise in SHBG
  - Statins lower SHBG

# Who Should Have Their T Tested?

- All patient with type 2 diabetes who present with erectile dysfunction
- Patients with clear and unequivocal symptoms of hypogonadism
- Patients suspected of primary or central hypogonadism due to other clinical conditions

# Potential Risks of Long Term T Deficiency in Men with T2DM

- Increased risk of premature cardiovascular morbidity and mortality
- Osteoporosis
- Increased incidence of respiratory disease
- Falls
- Sarcopaenia

# When to Start Treatment?

- Depends on a combination of TT / fT levels and symptoms
- Aim to get T levels into the reference range to start with
- If symptoms do not improve, aim to get T into the upper half of the reference range (but not above it)

# Potential Benefits of T Treatment in Men with T2DM

- Improvement in erectile dysfunction and sexual function
- Relief of other symptoms of hypogonadism
- Decrease in truncal adiposity
- Increase in insulin sensitivity
- Improved glycaemic control
- Decrease in total cholesterol
- Improved quality of life
- Improved psychological wellbeing

# Potential Side Effects of Testosterone Replacement

- Significant increase in haematocrit
- Increase in prostatic volume
- Increase in prostate specific antigen levels
- Dyslipidaemia
- Gynaecomastia
- Acne and oily skin
- Abnormalities of liver function tests associated with the use of oral preparations (not available in the UK or EU)
- Mood changes - aggression

# WARNING!

- **Supraphysiological levels can potentially aggravate latent or overt cardiac failure, stimulate appetite and cause weight gain, water and sodium retention, or priapism. The use of testosterone is contraindicated in male breast cancer and most forms of prostate cancer.**

# Stopping Criteria

- Absolute contraindications
  - The development of a sex hormone dependant malignancy e.g. prostate or breast cancer or a primary liver tumour
  - Unexplained rise in PSA
  - Unexplained hypercalcaemia
  - Nephrotic syndrome
  - Untreated obstructive sleep apnoea

# Stopping Criteria

- Relative contraindications
  - No clinical benefit is seen after 3 to 6 months of replacement (many patients can take up to 6 months to respond to benefits in erectile function).
  - Persistent elevation of haematocrit ( $>0.54$ ) which cannot be controlled by testosterone dose adjustment, change in testosterone formulation or regular venesection.
  - There are symptoms of lower urinary tract outflow obstruction
  - There are psychological problems, e.g. aggression, sexually inappropriate behaviour, depression or anxiety

# Methods of Delivery

- Should allow for titration
- Should be made after careful discussion with the patient
- Should be revisited frequently to discuss alternative methods of delivery

# Methods of Delivery

- Metered gel dispenser
- Gel satchets
- 3 monthly injections
- Monthly injections
- Buccal
- Oral

# Monitoring

- At 3, 6 and 12 months and annually thereafter
  - Full blood count (haemoglobin and haematocrit)
  - Liver function tests (especially with oral preparations)
  - Fasting lipid profile
  - Prostate specific antigen

# In summary

- Hypogonadism in T2DM is common
- The presence of ED should be recoded at each Annual Review, and if it is 'an issue' then should be investigated
- TRT may improve metabolic control