

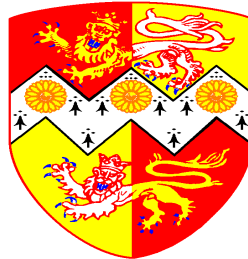
The Management of Hypogonadism in the Diabetic Patient

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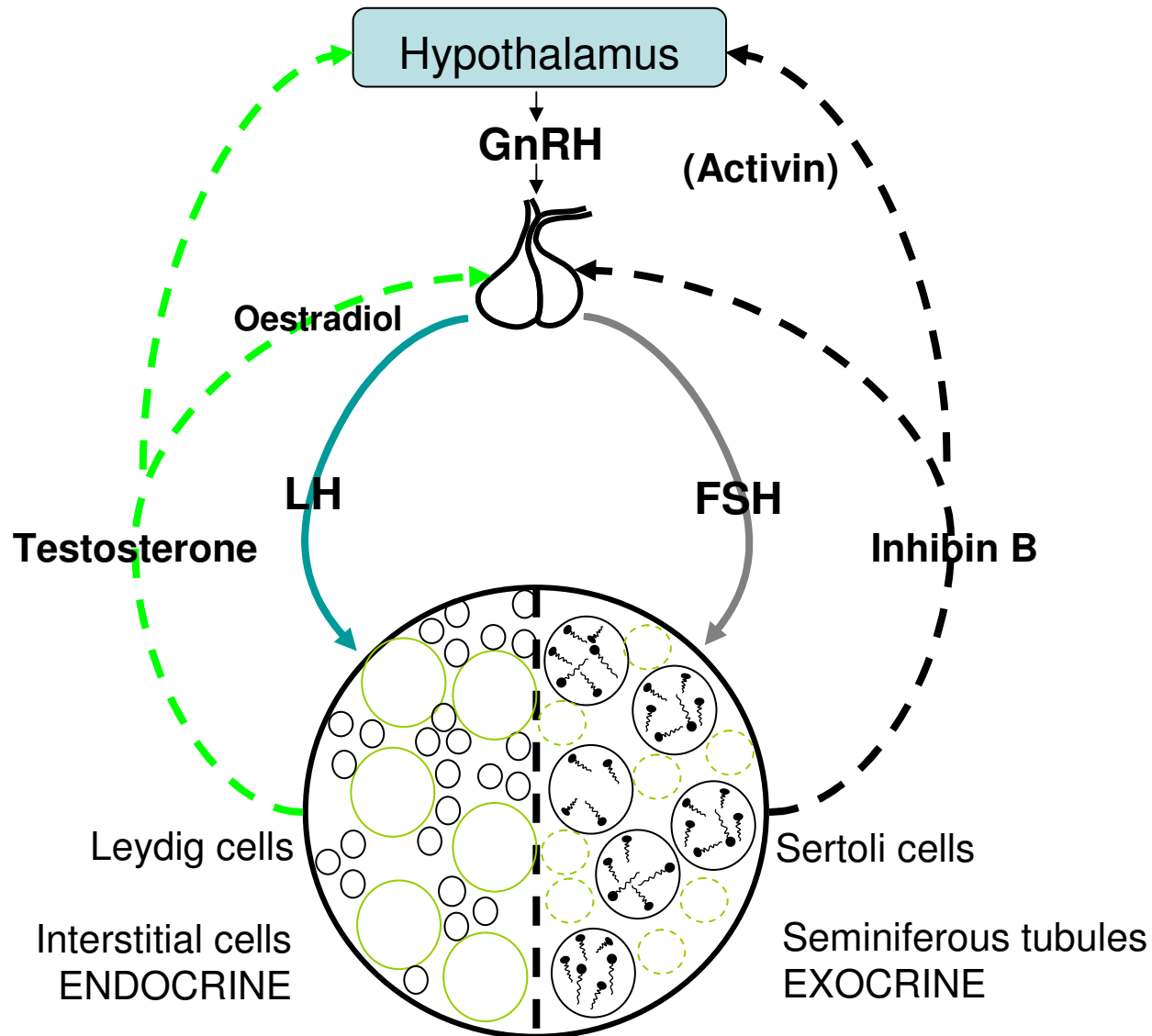
Norfolk & Norwich University Hospital NHS Foundation Trust



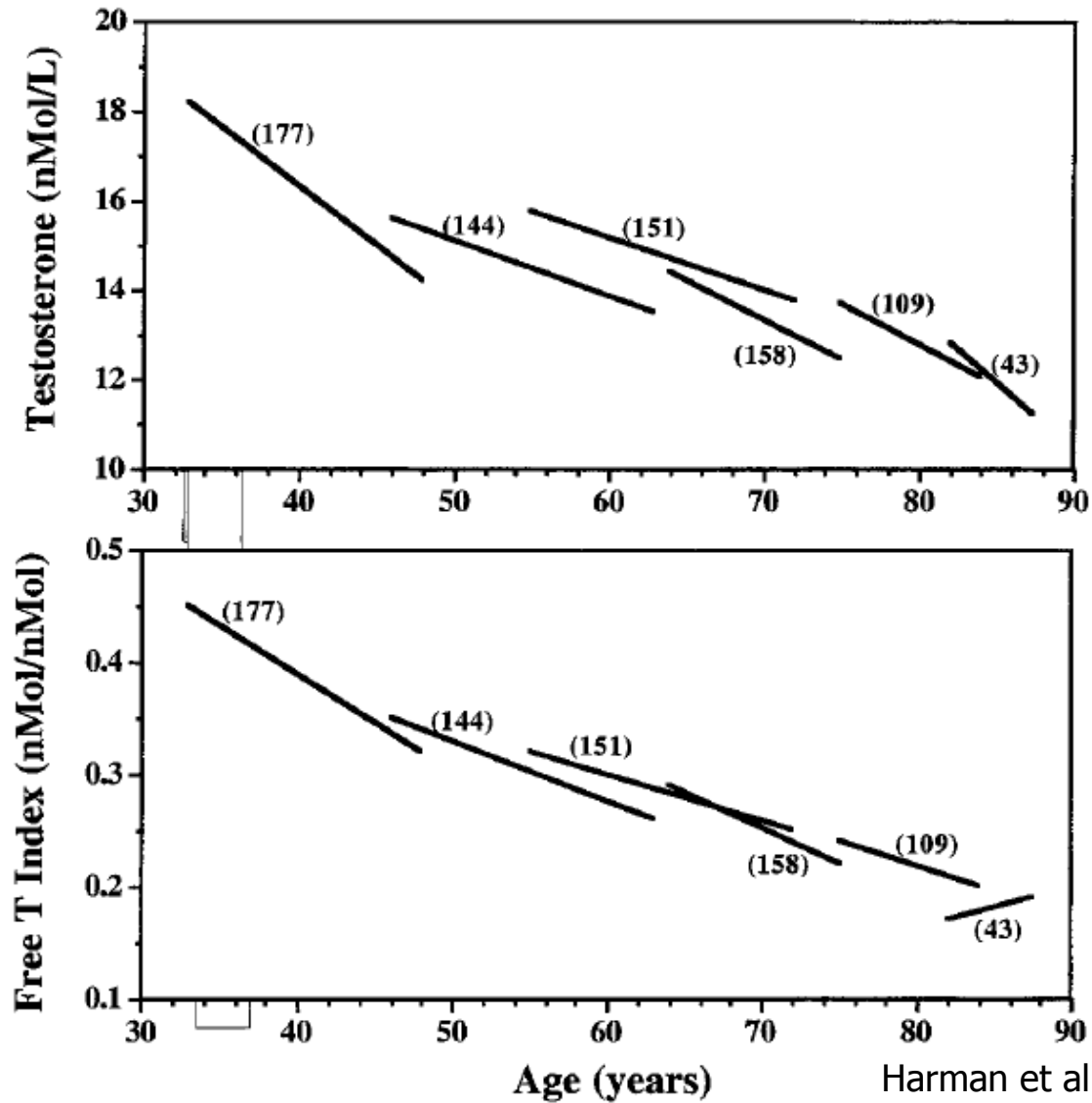
Definition

- 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

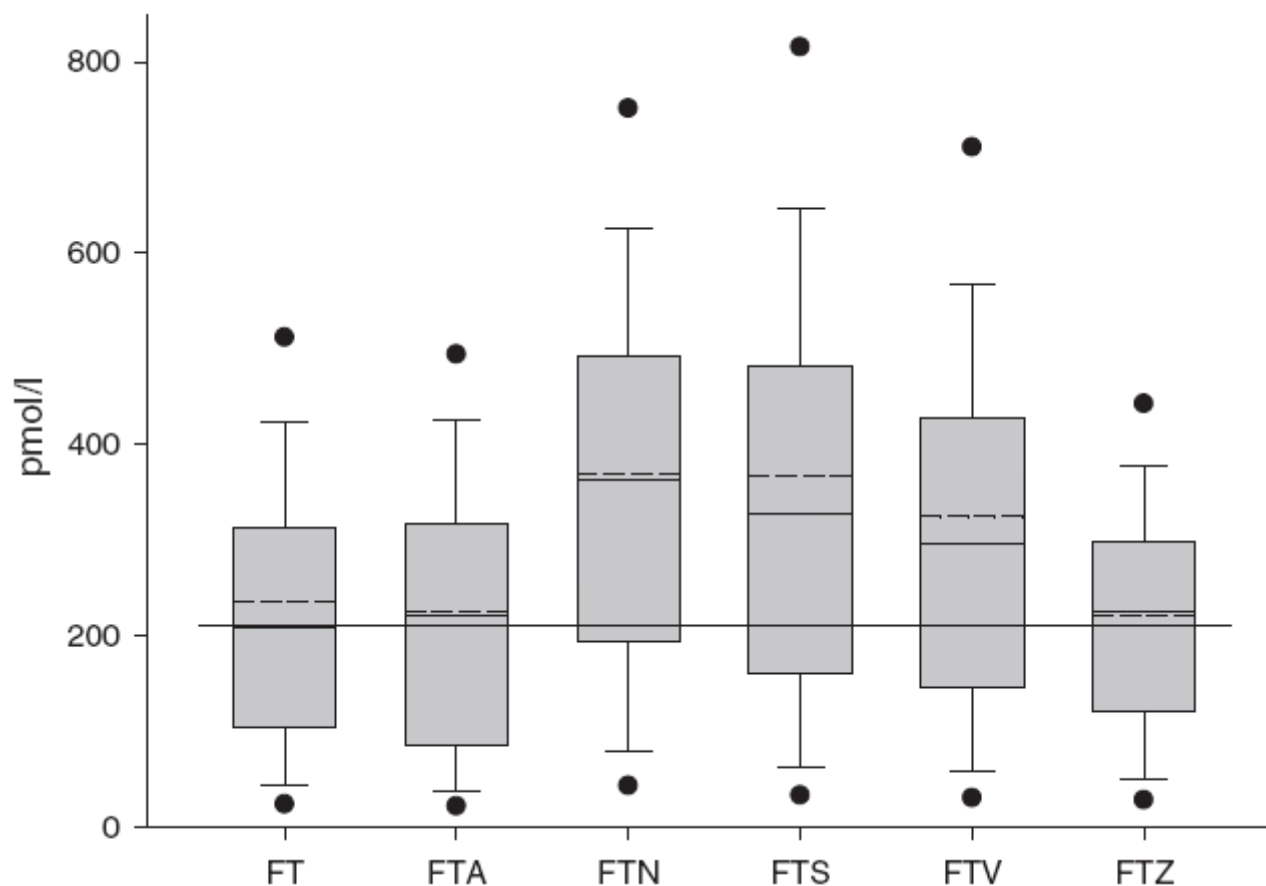
Wang C et al. J Androl 2009; 30: 1-9

Bhasin S et al JCEM 2010; 95: 2536-2559

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

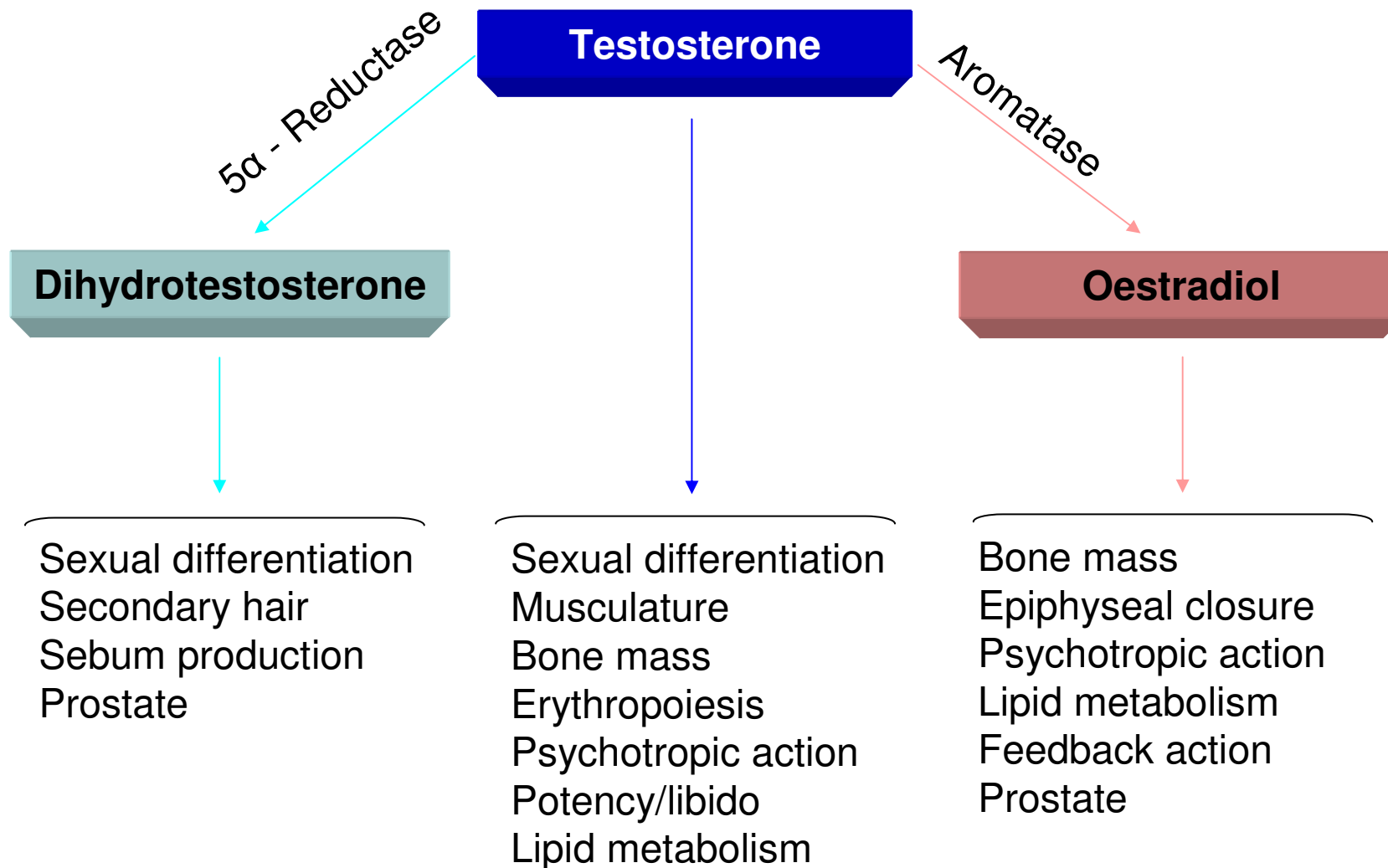
Obesity and Testosterone

- 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

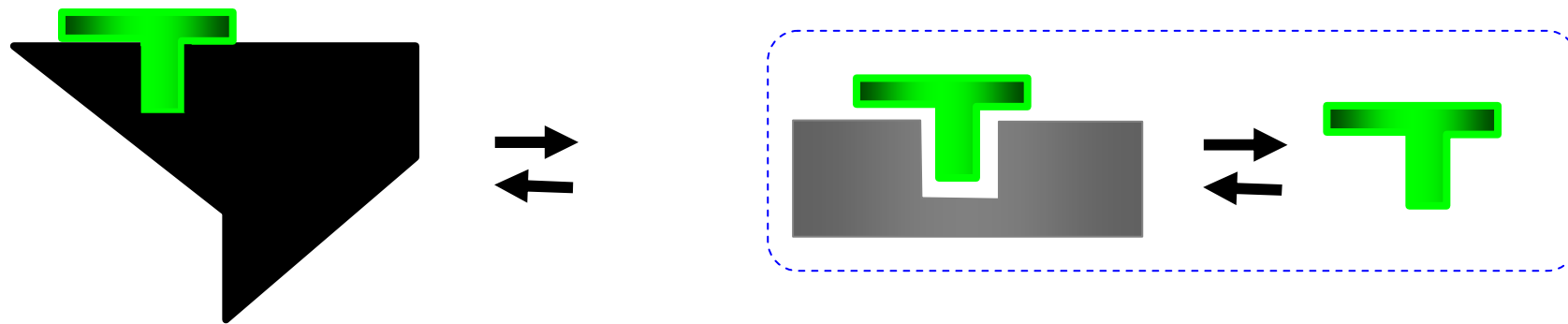
Testosterone and its Metabolites



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

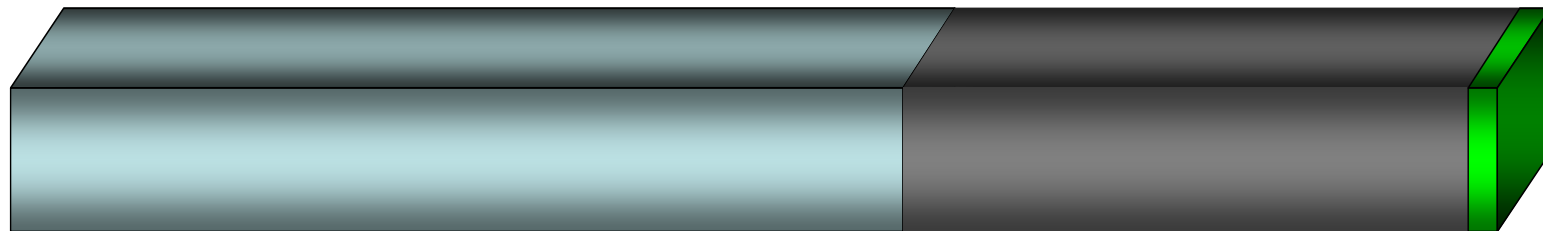
Binding of Testosterone



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