BIOCHEMICAL TESTS FOR THE INVESTIGATION OF COMMON ENDOCRINE PROBLEMS IN THE MALE

The purpose of this protocol is to describe common tests used for the investigation of endocrine problems in the male.

Related documents

BS/CB/DCB/EN/19 Biochemical Investigation of Suspected Endocrine Problems in Females

Specific Investigations:

Testosterone

Testosterone is important for general as well as sexual health in men. Symptoms of deficiency include decreased libido, loss of morning erections and erectile dysfunction but may also involve tiredness, weakness and depression.
Hypogonadism is defined by the clinical presentation and biochemical evidence of testosterone deficiency.

Samples for total serum testosterone should be measured before 11am as there is marked circadian rhythm, and on a fasting sample as testosterone levels may be suppressed by food intake or glucose. A level below the reference range on two occasions support the diagnosis of hypogonadism, although when the level is borderline adding an SHBG to calculate free testosterone will help clarify (test code FTES in Winpath, reference range 0.2 – 0.64 nmol/L).

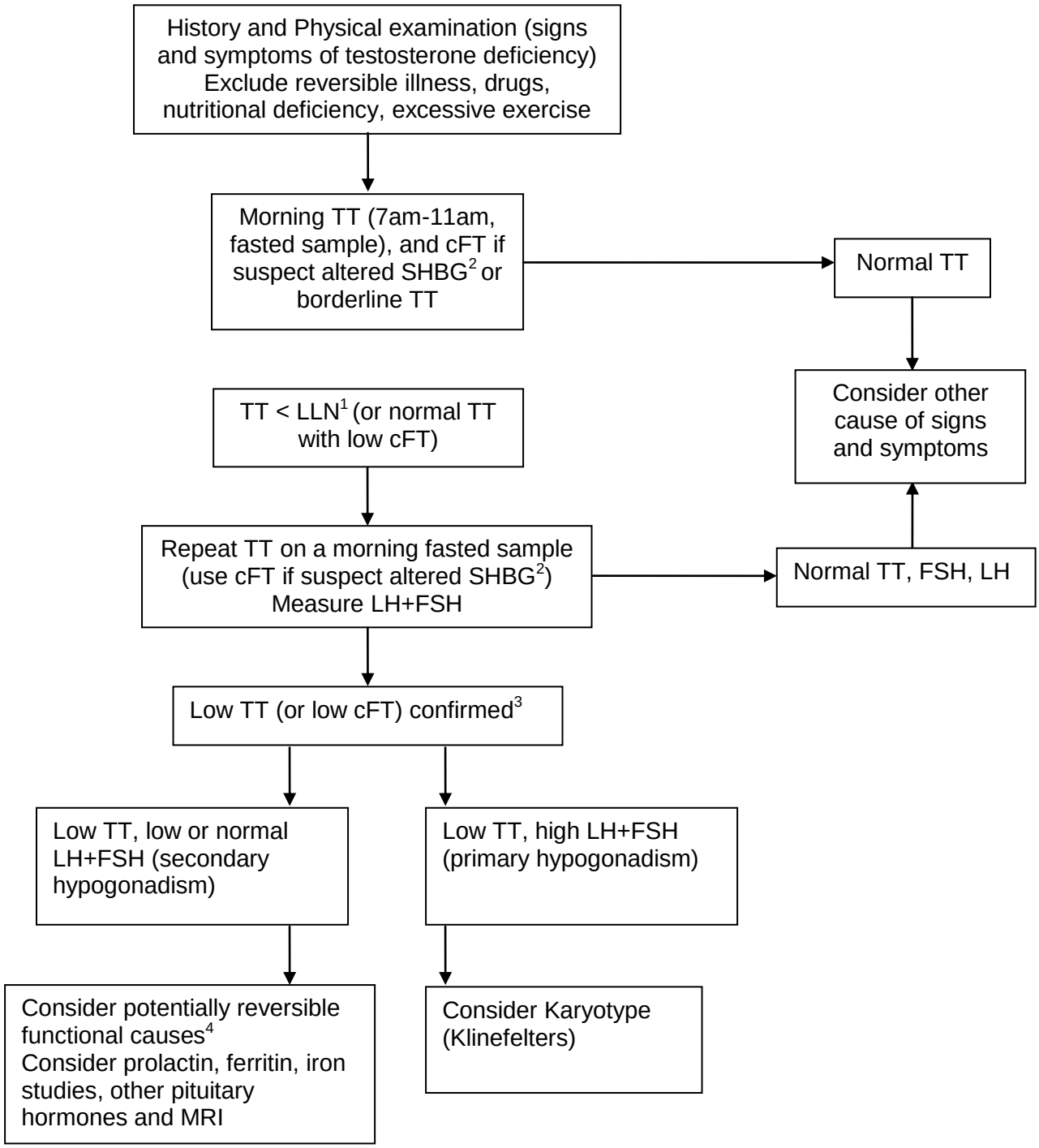
Additional investigations include measurement of gonadotrophins and prolactin.

LH/FSH- should be measured if low testosterone to differentiate between primary or secondary hypogonadism. NB: Consider other pituitary hormones if pituitary insufficiency is considered and iron studies for diagnosis of haemochromatosis.

Reference ranges currently in use (Males)

	FSH (IU/L)	LH (IU/L)	Testosterone (nmol/L)	Prolactin (mU/L)
Serum	up to 6	1.6 - 9.6	8.7 - 29	up to 700

Approach to the Diagnosis of Androgen Deficiency in Men



Abbreviations: TT – total testosterone, cFT – calculated free testosterone (Vermeulen), LLN – lower limit of normal

Notes

[1] – Endocrine Society Practice Guidelines (2018) do not define an absolute value below which the pathway should be followed due to variation in assay reference ranges.

European guidelines state:-

TT >12nmol/L - no testosterone deficiency
TT < 8nmol/L - testosterone deficiency } Repeat to confirm
TT 8-12 nmol/L - repeat with SHBG

A free testosterone <0.225 pmol/L can provide supportive evidence for treatment.

[2] - Table 1: Conditions associated with alterations of SHBG

Low SHBG	High SHBG
Obesity	Aging
Nephrotic syndrome	Liver disease
Hypothyroidism	Hyperthyroidism
Use of glucocorticoids, progestins, steroids	Anticonvulsants
Acromegaly	HIV
Diabetes	Use of oestrogens
Polymorphisms in the SHBG gene	Polymorphisms in the SHBG gene

[3] – Testosterone levels decline 1% per year from the age of 30 years and Roche quote an age related reference range –

TT 20-49y 8.7-29 nmol/L
>50y 6.7-26 nmol/L

cFT 20-49y 0.2-0.64 pmol/L
>50y 0.2-0.47 pmol/L

However, guidelines for the elderly population define a 'low testosterone' as below that of the young healthy adult male reference range.

A symptom-based study (Wu et al, 2010) defined late onset hypogonadism as the presence of at least 3 sexual symptoms and a fT <0.220 nmol/L in the elderly. Note 'elderly' is generally defined as >40y.

[4] – Table 2: Causes of primary and secondary hypogonadism

Causes Primary Hypogonadism

Hypergonadotrophic hypogonadism: High LH & FSH and Low testosterone

Klinefelters	Orchitis
Cryptorchidism	Advanced age
Myotonic dystrophy	Mutations in FSH/LH receptor genes
Anorchia	Varicocele
Some cancers	Androgen synthesis disorders
Chemotherapy	
Orchidectomy	

Infection	Environmental toxins	Illness
Radiation	Trauma	Idiopathic
Alkylating agents	Testicular torsion	Surgery
Suramin	Autoimmune	Glucocorticoids
Ketoconazole	Varicocele	End-stage renal disease*

Causes Secondary Hypogonadism

Hypogonadotrophic hypogonadism: Low LH & FSH and Low testosterone

Mutations	Infiltrative/destructive disease of hypothalamus/ pituitary
Hypothalamic/pituitary tumours	Idiopathic hypogonadotrophic hypogonadism
Iron overload syndromes	

Hyperprolactinaemia	Diabetes
Opiates	Systemic illness*
Anabolic steroids	Nutritional deficiency/excessive exercise
Glucocorticoids	Severe obesity
Alcohol/marijuana abuse*	Organ failure (liver/heart/lung)*
Some sleep disorders	Comorbid illness associated with aging*
Trauma	
Infection	

***** Combined primary and secondary hypogonadism, but classified to usual predominant hormonal pattern

[5] – Treatment guidelines

TT<8nmol/L - treatment usually beneficial
TT>12nmol/L - not hypogonadal
TT 8-12 nmol/L - short 3 month trial if cFT is low

Note these are largely based on the opinion of experts and are not evidence based.

Erectile dysfunction

Recommended tests include prolactin, LH/FSH, testosterone and thyroid function tests.

The Investigation of Gynaecomastia

Gynaecomastia is the enlargement of glandular tissue of the breast resulting from an increase in the effective oestrogen:androgen ratio within this tissue.

Recommended investigations include LH and FSH, oestradiol, testosterone, SHBG, HCG, thyroid function tests and prolactin. Chromosome analysis may also be indicated.

Certain drugs can also cause this condition (see Appendix 1) though ingestion of these drugs should not exclude further investigation.

The Investigation of Infertility/Subfertility

The male factor accounts for 25% of infertility. Couples should be referred after 1 year of unprotected sexual intercourse or sooner if there is a known cause for infertility or the woman is older than 36 years old.
In the male, causes of infertility include hormonal problems, defects in sperm synthesis or anatomical conditions. The key investigations involve semen analysis and hormonal measurements.

The results of the semen analysis conducted as part of an initial assessment should be compared with the World Health Organization reference values (NICE QS73):

- semen volume: 1.5 ml or more
- pH: 7.2 or more
- sperm concentration: 15 million spermatozoa per ml or more
- total sperm number: 39 million spermatozoa per ejaculate or more
- total motility (percentage of progressive motility and non-progressive motility):
- 40% or more motile or 32% or more with progressive motility
- vitality: 58% or more live spermatozoa
- sperm morphology (percentage of normal forms): 4% or more.

If any of the above criteria are abnormal repeat ideally after 3 months. If a gross deficiency is detected, analysis should be repeated within 2-4 weeks.

Azoospermia may be due to hypothalamic-pituitary failure (1%), primary testicular failure or obstruction to the genital tract. Useful investigations include LH, prolactin and a cystic fibrosis screen (sweat test or mutational analysis).

Oligozoospermia may be due primary testicular failure (also a cause of azoospermia). Conditions associated with this condition include cryptorchidism, torsion, trauma, orchitis, chromosome disorders, systemic disease, radio or chemo therapy though the majority of causes are unknown. Useful investigations include FSH, testosterone (9am sample), prolactin, LH and chromosome analysis.

Testosterone - Where the testosterone is low or low normal, a repeat measurement (at 9am due to diurnal variation) may be helpful with a request for SHBG.

References

- NICE Guideline (CG156) Feb 2013; Fertility problems: assessment and treatment
- NICE Quality Standard (QS73) October 2014; Fertility problems
- Bhasin S. et al. Testosterone Therapy in Men with Hypogonadism: an Endocrine Society Clinical Practice Guideline. *J Clin Endo Metab* 2018; **103**(5): 1715-1744.
- Ismail AAA and Barth JH. Endocrinology of gynaecomastia. *Ann Clin Biochem* 2001; **38**: 596-607.
- Jones TH. Late onset hypogonadism. *BMJ* 2009; **338**: 785-6.
- Wang C. et al. Investigation, treatment and monitoring of late-onset hypogonadism in males: ISA, ISSAM, EAU, EAA and ASA recommendations. *Eur J Endo* 2008; **159**: 7-14.
- Wu FCW et al. Identification of late-onset hypogonadism in middle aged and elderly men. *N Engl J Med* 2010; **363**(2): 123-35.

Appendix 1: Drugs known to cause gynecomastia in some men

Mode of action	Drugs
Metabolised to oestrogen, oestrogen activity or activates oestrogen production	Steroids, synthetic oestrogens, hCG, digoxin, clomiphene, phenytoin, diazepam
Anti-androgen activity or reduces androgen production	Ketoconazole, metronidazole, cimetidine, ranitidine, omeprazole, spironalactone, flutamide, bicalutamide, cytotxic drugs, methotrexate, penicillamine.
Causes hyperprolactinaemia	Metoclopramide, domperodone, haloperidol, phenothiazine
Increased metabolism and clearance of androgens	Alcohol
Increased SHBG	Phenytoin, diazepam

Appendix 2: Guidelines for Monitoring Patients Receiving Testosterone Replacement

Table 9. Monitoring Men Receiving T Therapy

- Explain the potential benefits and risks of monitoring for prostate cancer and engage the patient in shared decision making regarding the prostate monitoring plan.
- Evaluate the patient at 3–12 mo after treatment initiation and then annually to assess whether symptoms have responded to treatment and whether the patient is suffering from any adverse effects
- Monitor T concentrations 3–6 mo after initiation of T therapy:
  - Therapy should aim to raise serum T concentrations into the mid-normal range.
    - Injectable T enanthate or cypionate: measure serum T concentrations midway between injections. If mid-interval T is >600 ng/dL (24.5 nmol/L) or <350 ng/dL (14.1 nmol/L), adjust dose or frequency.
    - Transdermal gels: assess T concentrations 2–8 h following the gel application, after the patient has been on treatment for at least 1 wk; adjust dose to achieve serum T concentrations in the mid-normal range.
    - Transdermal patches: assess T concentrations 3–12 h after application; adjust dose to achieve T concentration in the mid-normal range.
    - Buccal T bioadhesive tablet: assess concentrations immediately before or after application of fresh system.
    - T pellets: measure T concentrations at the end of the dosing interval. Adjust the number of pellets and/or the dosing interval to maintain serum T concentrations in the mid-normal range.
    - Oral T undecanoate[a]: monitor serum T concentrations 3–5 h after ingestion with a fat-containing meal.
    - Injectable T undecanoate: measure serum T levels at the end of the dosing interval just prior to the next injection and aim to achieve nadir levels in low-mid range.
- Check hematocrit at baseline, 3–6 mo after starting treatment, and then annually. If hematocrit is >54%, stop therapy until hematocrit decreases to a safe level; evaluate the patient for hypoxia and sleep apnea; reinitiate therapy with a reduced dose.
- Measure BMD of lumbar spine and/or femoral neck after 1–2 y of T therapy in hypogonadal men with osteoporosis, consistent with regional standard of care.
- For men 55–69 years of age and for men 40–69 years of age who are at increased risk for prostate cancer who choose prostate monitoring, perform digital rectal examination and check PSA level before initiating treatment; check PSA and perform digital rectal examination 3–12 mo after initiating T treatment, and then in accordance with guidelines for prostate cancer screening depending on the age and race of the patient.
- Obtain urological consultation if there is:
  - An increase in serum PSA concentration >1.4 ng/mL within 12 mo of initiating T treatment
  - A confirmed PSA > 4 ng/mL at any time
  - Detection of a prostatic abnormality on DRE
  - Substantial worsening of LUTS
- Evaluate formulation-specific adverse effects at each visit as per Table 5.

Adapted with permission from Bhasin *et al.* (7).