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. A level below the reference range on two occasions support the diagnosis of hypogonadism although when the level is borderline calculating free testosterone will help clarify (Calculator using the Vermeulen equation is available at http://www.issam.ch/freetesto.htm, please ensure the correct units for albumin and testosterone are selected)

Coded comment `SHBM – Calculated free testosterone reference range in men 0.20-0.64nmol/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)

<table>
<thead>
<tr>
<th></th>
<th>FSH (IU/L)</th>
<th>LH (IU/L)</th>
<th>Testosterone (nmol/L)</th>
<th>Prolactin (mU/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum</td>
<td>up to 6</td>
<td>1.6 - 9.6</td>
<td>8.7 - 29</td>
<td>up to 700</td>
</tr>
</tbody>
</table>
Approach to the Diagnosis of Androgen Deficiency in Men

**History and Physical examination (signs and symptoms)**

**Morning TT (7am-11am)**

- **Normal TT**
  - **Follow up**

- **TT ≤ LLN**
  - Exclude reversible illness, drugs, nutritional deficiency, excessive exercise
  - Repeat TT (use cFT if suspect altered SHBG)
  - LH+FSH

- **Low TT confirmed**
  - **Normal TT, FSH, LH**
    - Low TT, low or normal LH+FSH (secondary hypogonadism)
      - Consider PRL, ferritin, iron studies, other pituitary hormones and MRI
    - Low TT, high LH+FSH (primary hypogonadism)
      - Consider Karyotype (Klinefelters)

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

1 – Endocrine Society Practice Guidelines (2010) do not define an absolute value below which the pathway should be followed due to variation in assay reference ranges.

European guidelines state:

- TT > 12 nmol/L - no testosterone deficiency
- TT < 8 nmol/L - testosterone deficiency
- TT 8-12 nmol/L - repeat with SHBG

Repeat to confirm

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

2. Table 1: Conditions associated with alterations of SHBG

<table>
<thead>
<tr>
<th>Low SHBG</th>
<th>High SHBG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obesity</td>
<td>Aging</td>
</tr>
<tr>
<td>Nephrotic syndrome</td>
<td>Liver disease</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>Hyperthyroidism</td>
</tr>
<tr>
<td>Use of glucocorticoids, progestins, steroids</td>
<td>Anticonvulsants</td>
</tr>
<tr>
<td>Acromegaly</td>
<td>HIV</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Use of oestrogens</td>
</tr>
</tbody>
</table>

3 – In the elderly, 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 by Wu et al. 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.

5 – Treatment guidelines

- TT < 8 nmol/L - treatment usually beneficial
- TT > 12 nmol/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.
Causes Primary Hypogonadism
Hypergonadotrophoc hypogonadism: High LH FSH and Low testosterone

<table>
<thead>
<tr>
<th>Congenital Abnormalities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Klinefelters</td>
</tr>
<tr>
<td>Varicocele</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Acquired Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection</td>
</tr>
<tr>
<td>Radiation</td>
</tr>
<tr>
<td>Alkylating agents</td>
</tr>
<tr>
<td>Suramin</td>
</tr>
<tr>
<td>Ketoconazole</td>
</tr>
</tbody>
</table>

Causes Secondary Hypogonadism
Hypogonadotrophi hypogonadism: Low LH FSH and low testosterone

<table>
<thead>
<tr>
<th>Congenital Abnormalities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mutations</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Acquired</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gonadotrophin Suppression</strong></td>
</tr>
<tr>
<td>Hyperprolactinaemia</td>
</tr>
<tr>
<td>Steroids</td>
</tr>
<tr>
<td>Illness</td>
</tr>
<tr>
<td>Opiates</td>
</tr>
</tbody>
</table>

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 semen analysis conducted as part of an initial assessment should be compared with the following World Health Organization reference values\(^2\):

- 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 2014 Fertility pages 20 & 21
Appendix 1: Drugs known to cause gynecomastia in some men

<table>
<thead>
<tr>
<th>Mode of action</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolised to oestrogen, oestrogen activity or activates oestrogen production</td>
<td>Steroids, synthetic oestrogens, hCG, digoxin, clomiphene, phenytoin, diazepam</td>
</tr>
<tr>
<td>Anti-androgen activity or reduces androgen production</td>
<td>Ketoconazole, metronidazole, cinetidine, ranitidine, omeprazole, spironalactone, flutamide, bicalutamide, cytotoxic drugs, methotrexate, penicillamine.</td>
</tr>
<tr>
<td>Causes hyperprolactinaemia</td>
<td>Metoclopramide, domperodone, haloperidol, phenothiazine</td>
</tr>
<tr>
<td>Increased metabolism and clearance of androgens</td>
<td>Alcohol</td>
</tr>
<tr>
<td>Increased SHBG</td>
<td>Phenytoin, diazepam</td>
</tr>
</tbody>
</table>
Appendix 2: Guidelines for Monitoring Patients Receiving Testosterone Replacement

TABLE 8. Monitoring men receiving testosterone therapy

1. Evaluate the patient 3 to 6 months after treatment initiation and then annually to assess whether symptoms have responded to treatment and whether the patient is suffering from any adverse effects.

2. Monitor testosterone level 3 to 6 months after initiation of testosterone therapy:
   - Therapy should aim to raise serum testosterone level into the mid-normal range.
   - Injectable testosterone enanthate or cypionate: Measure serum testosterone level midway between injections. If testosterone is >700 ng/dl (24.5 nmol/l) or <400 ng/dl (14.1 nmol/l), adjust dose or frequency.
   - Transdermal patches: Assess testosterone level 3–12 h after application of the patch; adjust dose to achieve testosterone level in the mid-normal range.
   - Buccal testosterone bioadhesive tablet: Assess level immediately before or after application of fresh system.
   - Transdermal gels: Assess testosterone level any time after patient has been on treatment for at least 1 wk; adjust dose to achieve serum testosterone level in the mid-normal range.
   - Testosterone pellets: Measure testosterone levels at the end of the dosing interval. Adjust the number of pellets and/or the dosing interval to achieve serum testosterone levels in the normal range.
   - Oral testosterone undecanoate*: Monitor serum testosterone level 3 to 5 h after ingestion.
   - Injectable testosterone undecanoate*: Measure serum testosterone level just prior to each subsequent injection and adjust the dosing interval to maintain serum testosterone in mid-normal range.

3. Check hematocrit at baseline, at 3 to 6 months, and then annually. If hematocrit is >54%, stop therapy until hematocrit decreases to a safe level; evaluate the patient for hypoxia and sleep apnea; reintroduce therapy with a reduced dose.

4. Measure bone mineral density of lumbar spine and/or femoral neck after 1–2 yr of testosterone therapy in hypogonadal men with osteoporosis or low trauma fracture, consistent with regional standard of care.

5. In men 40 years of age or older with baseline PSA greater than 0.6 ng/ml, perform digital rectal examination and check PSA level before initiating treatment, at 3 to 6 months, and then in accordance with guidelines for prostate cancer screening depending on the age and race of the patient.

6. Obtain urological consultation if there is:
   - An increase in serum PSA concentration >1.4 ng/ml within any 12-month period of testosterone treatment.
   - A PSA velocity of >0.4 ng/ml/yr using the PSA level after 6 months of testosterone administration as the reference (only applicable if PSA data are available for a period exceeding 2 yr).
   - Detection of a prostatic abnormality on digital rectal examination.
   - An AUA/ IPSS prostate symptom score of >19.

7. Evaluate formulation-specific adverse effects at each visit:
   - Buccal testosterone tablets: Inquire about alterations in taste and examine the gums and oral mucosa for irritation.
   - Injectable testosterone esters (enanthate, cypionate, and undecanoate): Ask about fluctuations in mood or libido, and rarely cough after injections.
   - Testosterone patches: Look for skin reaction at the application site.
   - Testosterone gels: Advise patients to cover the application sites with a shirt and to wash the skin with soap and water before having skin-to-skin contact, because testosterone gels leave a testosterone residue on the skin that can be transferred to a woman or child who might come in close contact. Serum testosterone levels are maintained when the application site is washed 4–6 h after application of the testosterone gel.
   - Testosterone pellets: Look for signs of infection, fibrosis, or pellet extrusion.

* Not approved for clinical use in the United States.

AUA/IPSS = American Urological Association International Prostate Symptom Score, PSA = prostate-specific antigen