Monitoring in TRT
According to EAU Guidelines 2015
Personal Experience

Herman Leliefeld, Urologist / Andrologist
The Netherlands

PRISM Bruges
25-26 June 2015
Guidelines on Male Hypogonadism

G.R. Dohle (Chair), S. Arver, C. Bettocchi, T.H. Jones, S. Kliesch, M. Punab
Monitoring TRT according to EAU Guidelines

Should be focused on:

• Safety

• Recognition of adverse effects of treatment

• Efficacy by aiming physiological Testosterone levels in order to alleviate the clinical symptoms of testosterone deficiency
Monitoring TRT according to EAU Guidelines

The physician should be well informed about:

• Physiological effects of Testosterone on the various Endorgans

• The various T preparations, who differ in route of administration and pharmacokinetics

The selection should be a joint decision by both patient and doctor
Monitoring TRT according to EAU Guidelines

• Testosterone has influence on many endorgans / functions:

- sexuality
- mood/energy/well-being
- bones
- prostate
- metabolism
- body composition
Monitoring TRT according to EAU Guidelines

• History-taking is essential:
  
  - general feelings; well-being
  - mental and physical activities
  - mood, moodswings
  - libido, sexual desire
  - erections, morning erections, sexual thoughts
  - sexual activities
  - hot flushes

• Published Questionnaires are unreliable and have low specificity
Monitoring TRT according to EAU Guidelines

• Testosterone level

  - insufficient data to define optimal serum levels of T during TRT

  - according to expert opinion: mid-normal range of healthy men

    17-20 nmol/l = 4.90-5.8 ng/ml

  - optimal point of time to measure T is dependent on the formulation of TRT used
T blood levels monitoring depending on formulation

Short-acting:

- **Enanthate/Cyp. T inj**  
  Between 2 injections, and/or after 2 or 3 weeks

Long-acting:

- **Undecanoate T inj**  
  Just before next injection; every 10-14 weeks

- **Gels: natural T**  
  2 to 8 hours after application  
  more than 2 weeks after starting the treatment

- **Undecanoate T per os**  
  3 to 5 hours after ingestion

*Buvat J et al.*  
*J Sex Med 2013; 10: 245-284*
Breakfast
- two rolls
- two slices of cheese
- two slices of ham (20 g)
- butter (20 g)
- two cups of caffeine-free coffee

FASTING

Testosterone Undecanoate 2 capsules 40 mg

Bagchus et al., Pharmacotherapy. 2003; 23:319
Stable and physiological T-concentration

Testosterone nmol/l

Time in hours

- BASELINE
- ANDROGEL 50 mg (1 sachet)
- ANDROGEL 100 mg (2 sachets)
Long acting versus short acting


SUSTANON
NETIDO
TRT with testosterone undecanoate in castor oil

Zitzmann., Aging Male 9 (Suppl 1):5; 2006
TRT with testosterone undecanoate in castor oil

• Testosterone between 10-15 nmol/l  every 12 weeks
• Testosterone < 10 nmol/l  every 10 weeks
• Testosterone > 15 nmol/l  every 14 weeks
Table 7: Testosterone preparations for replacement therapy

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Administration</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Testosterone undecanoate</td>
<td>Oral; 2-6 cps every 6 h</td>
<td>Absorbed through the lymphatic system, with consequent reduction of liver involvement.</td>
<td>Variable levels of testosterone above and below the mid-range [69]. Need for several doses per day with intake of fatty food.</td>
</tr>
<tr>
<td>Testosterone cypionat</td>
<td>Intramuscular; one injection every 2-3 weeks</td>
<td>Short-acting preparation that allows drug withdrawal in case of onset of side-effects.</td>
<td>Possible fluctuation of testosterone levels [72, 73].</td>
</tr>
<tr>
<td>Testosterone enanthate</td>
<td>Intramuscular; one injection every 2-3 weeks</td>
<td>Short-acting preparation that allows drug withdrawal in case of onset of side-effects.</td>
<td>Fluctuation of testosterone levels [72, 73].</td>
</tr>
<tr>
<td>Testosterone undecanoate</td>
<td>Intramuscular; one injection every 10-14 weeks</td>
<td>Steady-state testosterone levels without fluctuation.</td>
<td>Long-acting preparation that cannot allow drug withdrawal in case of onset of side-effects [74].</td>
</tr>
<tr>
<td>Transdermal testosterone</td>
<td>Gel or skin patches; daily application</td>
<td>Steady-state testosterone level without fluctuation.</td>
<td>Skin irritation at the site of application and risk of interpersonal transfer [75, 76].</td>
</tr>
</tbody>
</table>

| Sublingual testosterone | Sublingual; daily doses | Rapid absorption and achievement of physiological serum level of testosterone. | Local irritation [80, 81]. |
| Buccal testosterone | Buccal tablet; two doses per day | Rapid absorption and achievement of physiological serum level of testosterone. | Irritation and pain at the site of application [80, 81]. |
| Subdermal depot | Subdermal implant every 5-7 months | Long duration and constant serum testosterone level. | Risk of infection and extrusion of the implants [69, 82, 83]. |
Monitoring TRT according to EAU Guidelines

- Bone density: monitoring only in men whose BMD was abnormal before initiation of TRT

- Haematocrit: elevated Ht is the most frequent side-effect of TRT; stay < 0.54
  - clinical significance: unclear; trombosis?
  - erythrocytosis: evident at 3 months, peaks at 12 months
  - use no or minimal venous occlusion on taking bloodsample

- Cardiovasc.: caution in men with pre-existing CVD; fluid retention possible
Erythrocytosis and Polycythemia secondary to TRT in the Aging Male

• Risk for erythrocytosis increases to 315%; most frequent adverse event
• Advice: avoid im injections in risk groups:
  obese men,
  aging,
  smokers,
  T2DM and lipids ↑
• Inconclusive evidence for Veno-Thrombo-Embolism (VTE)
• Caused by suprafysiologica levels of T
Proposed mechanism by Bachman and Calado

Three major factors:

1. Increased erythropoietin (EPO)
2. Decreased hepcidin production
3. Bone marrow stimulation through increase of estradiol

Monitoring TRT according to EAU Guidelines

• Prostate safety: marginal increase in PSA and prostate volume, max at 1y

<table>
<thead>
<tr>
<th>Treatment (months)</th>
<th>PSA (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>0.0</td>
</tr>
<tr>
<td>6</td>
<td>0.5</td>
</tr>
<tr>
<td>12</td>
<td>0.5</td>
</tr>
<tr>
<td>18</td>
<td>1.0</td>
</tr>
<tr>
<td>24</td>
<td>1.5</td>
</tr>
<tr>
<td>30</td>
<td>1.5</td>
</tr>
<tr>
<td>36</td>
<td>2.0</td>
</tr>
</tbody>
</table>

• DRE: at 3, 6 and 12 months
• TRUS: optional

Wang C, J Clin Endo Metab 2004;89:2085-98
Time-dependent and symptom-specific onset of effects of testosterone substitution
## Recommendations for follow-up  EAU 2015

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>The response to treatment should be assessed 3, 6 and 12 months after the onset of treatment, and thereafter annually.</td>
<td>4</td>
<td>C</td>
</tr>
<tr>
<td>Haematocrit should be monitored at 3, 6 and 12 months and thereafter annually. The testosterone dosage should be decreased, or therapy discontinued if the haematocrit increases above 0.54.</td>
<td>4</td>
<td>C</td>
</tr>
<tr>
<td>Prostate health should be assessed by digital rectal examination and PSA before the start of TRT. Follow-up by PSA at 3, 6 and 12 months and thereafter annually.</td>
<td>4</td>
<td>C</td>
</tr>
<tr>
<td>Men with cardiovascular diseases should be assessed for cardiovascular symptoms before TRT is initiated. There should be close clinical assessment during TRT.</td>
<td>1B</td>
<td>A</td>
</tr>
</tbody>
</table>

*BMD = bone mineral density; PSA = prostate-specific antigen; TRT = testosterone replacement therapy.*
Monitoring TRT according to EAU Guidelines

• Personal experience:

-physical examination: assessment of BMI
  waist circumference
  testicular volume
  gynecomastia
  hairloss
  DRE / TRUS

-labor-intensive; patient has often wrong ideas:
  -”I use it only in the weekends”

-blood sampling:
  -on the other arm as T-gel was applied
  -at the same time: 4 hours after application

-written information; no informed consent yet
Monitoring TRT according to EAU Guidelines

• Personal experience:

- skin irritation due to uptake enhancers: change the type of preparation
- start always with a gel instead of a long acting preparation
- short acting injections: higher risk for polycythaemia, more moodswings
- older men, obese men: higher risk for polycythaemia
- no check for fT on monitoring, unless there is a reason
- no check for liverfunction on monitoring: the oral 17α-methyltestosteron is not approved anymore
- no use of questionnaires on FU

Zitzmann, J Clin Endocrinol Metab, 2007: 92:3844-53
Keep always in mind:

### Table 6: Contraindications against testosterone treatment

<table>
<thead>
<tr>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate cancer</td>
</tr>
<tr>
<td>Male breast cancer</td>
</tr>
<tr>
<td>Severe sleep apnoea</td>
</tr>
<tr>
<td>Male infertility-active desire to have children</td>
</tr>
<tr>
<td>Haematocrit &gt; 0.54%</td>
</tr>
<tr>
<td>Severe lower urinary tract symptoms due to benign prostatic hyperplasia</td>
</tr>
<tr>
<td>Severe chronic cardiac failure/New York Heart Association Class IV</td>
</tr>
</tbody>
</table>
Effects of T gel (after 3 months) on sperm characteristics in 18 hypogonadal men

<table>
<thead>
<tr>
<th></th>
<th>Before</th>
<th>On treatment</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Testosterone, nmol/L</td>
<td>8.4 [7.6–11.2]</td>
<td>16.25 [15.3–18.0]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SHBG, nmol/L</td>
<td>32.4 [24.4–40.8]</td>
<td>32.75 [25.5–40.2]</td>
<td>0.81</td>
</tr>
<tr>
<td>Sperm volume, mL</td>
<td>2.05 [1.6–4.0]</td>
<td>2.6 [1.8–4.4]</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Concentration, mln/mL</td>
<td>19.0 [15.0–37.0]</td>
<td>23.0 [15.0–47.0]</td>
<td>0.24</td>
</tr>
<tr>
<td>Motility a + b, %</td>
<td>42.6 [18.0–47.0]</td>
<td>42.0 [25.0–51.0]</td>
<td>0.69</td>
</tr>
<tr>
<td>Normal morphology, %</td>
<td>24.0 [14.0–32.0]</td>
<td>15.0 [13.0–22.0]</td>
<td>0.06</td>
</tr>
<tr>
<td>Vitality, %</td>
<td>76.0 [65.0–86.0]</td>
<td>77.0 [58.0–81.0]</td>
<td>0.5</td>
</tr>
</tbody>
</table>

- In another study, treatment with IM testosterone injections led to a decline in LH, FSH and sperm concentration.
- Thus, treatment with IM testosterone forms should be avoided in patients who are planning to father a child in the next 2 years

Ms Khalaya et al. Gynecol Endocrinol
Published online August 28th
In case of fertility wish:

- Clomiphene citrate for male hypogonadism
- Dose: 3 times a week 50 mg or once a day
- Approved only for dysfunction of the ovaries
- Selective Estrogen Receptor Modulator (SERM)
- Blocking of the feedback inhibition of E2 at the level of the hypothalamus

Taylor F, J Sex Med 2010;7:269-76
Herman Leliefeld
Urologist/Andrologist

PRISM Bruges
25-26 June 2015
Case: man, 64 y

History in short:

ED : since half a year
Libido : diminished
Mood : depressed since years
Vitality : no energy
Sleep : disturbed
Relation : problematic;
Man 64 years; previous history:

- Hypertension
- Hypercholesterolaemia
- Depressions since many years
- Sleepapnoea with CPAP during the night
- Lumbar stenosis
- Medicines: many; bisopropol
Physical Exam / lab results:

- BMI: 28.1; Waist circumference: 108 cm
- RR: 156/93 mm Hg
- Genitals: normal; slight gynaecomastia
- DRE: normal

- Lab: 
  - T: 10.35 nmol/l
  - PSA: 1.1 μg/l
What would you do?
My action was:

• Starting with tadalafil, 5 mg once a day; patient refused TRT at first visit
• Changed bisopropol to nebivolol; called his general practitioner
• New visit after 6 weeks
• Before second visit: Second Testosterone
  SHBG
  LH
  FSH and Prolaktin
  Hb, Ht and ery’s
PDE5-inhibitors can increase T

No sex: T↓; LH↑

Fabbri, 1988
Carosa, 2002

With sex: T↑; LH↓

Carosa, 2004
Clin. Endocrinology

Table 1: Hormonal values before and after 3 months of impotence therapy

<table>
<thead>
<tr>
<th></th>
<th>T (nmol/l)</th>
<th>P vs. basal</th>
<th>P vs. Sild</th>
<th>FT (pmol/l)</th>
<th>P vs. basal</th>
<th>P vs. Sild</th>
<th>LH (IU/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before Sild</td>
<td>11.8±3.1</td>
<td>–</td>
<td>–</td>
<td>62.1±26.7</td>
<td>–</td>
<td>–</td>
<td>4.3±1.1</td>
</tr>
<tr>
<td>After Sild</td>
<td>16.3±4.2</td>
<td>0.000</td>
<td>–</td>
<td>75.2±18.4</td>
<td>0.010</td>
<td>–</td>
<td>3.1±1.1</td>
</tr>
<tr>
<td>Before Tad</td>
<td>11.4±2.8</td>
<td>–</td>
<td>0.297</td>
<td>56.2±20.8</td>
<td>–</td>
<td>0.142</td>
<td>5.0±1.9</td>
</tr>
<tr>
<td>After Tad</td>
<td>17.4±3.1</td>
<td>0.001</td>
<td>0.001</td>
<td>84.6±25.7</td>
<td>0.000</td>
<td>0.040</td>
<td>2.5±1.5</td>
</tr>
</tbody>
</table>

Fig. 1: Number of pills (pill) consumed and frequency of full sexual intercourse (sex) per month in sildenafil (Sild)- and tadalafil (Tad)-treated patients, as recorded by SEF diaries. *P = 0.036.
Testosterone and Sexual Intercourse

Jannini, 1999
After 6 weeks:

History:

- Good erections; no intercourse: dyspareunia
- Not satisfied: bad libido; memory-problems; mood not improved

Lab-results: second T : 10.90 nmol/l
    cFT : 205 pmol/l
    LH, FSH, PRL : normal
    Hb : 8.6 mmol/l (8.6-10.7)
    Ht : 0.42
What is your next action?
Araujo et al. J Clin Endocrinol Metabolism 2007,
Next action:

• Start androgel 50mg once a day for 3 months; continue tadalafil

• Explained possible risks / side effects
After 3 months:

Lab results:
- T : from 10.9 to 16.5 nmol/l
- Hb : from 8.6 to 9.2 mmol/l
- Ht : from 0.42 to 0.49
- PSA : from 1.1 to 1.3 μg/L

- Erections improved further; relation did not
- Libido improved
- Mood improved
- Memory?
This case raises the question: What to do first?

- Testosterone Replacement Therapy?
- PDE-5 Inhibitors?
- Or both directly?
Algorithm for TRT in ED-patients
A practical approach

• Start TRT in young men with low T: cure!

• Start PDE5-I’s in adult men with subnormal T:
  1. + check medication to be stopped
  2. + treat underlying conditions
  3. + add up TRT if T remains low (salvage)

• Start combined therapy in older men with ED, low T and comorbidities
Message on TRT and PDE5-I’s

• PDE5-I’s can restore erections
  - symptomatically
  - in days / weeks

• TRT can restore erections
  - as a cure
  - after several months

  can improve libido, ejaculation, mood within 1 month
  can improve metabolism, bone, muscle within 6 months
Herman Leliefeld
Urologist/Andrologist

PRISM Bruges
25-26 June 2015
**T blood levels monitoring**

- **Enanthate/Cyp. T inj**  
  Between 2 injections, and/or after 2 or 3 weeks

- **Undecanoate T inj**  
  Just before next injection

- **Implants**  
  Just before next injection

- **Patches**  
  *Daily:*  
  6 to 12 hours after application  
  *Matrical (2 days):*  
  13 to 36 hours after application

- **Gels**  
  2 to 8 hours after application  
  more than 2 weeks after starting the treatment

- **Axilar solution**  
  Same

- **Undecanoate T per os**  
  3 to 5 hours after ingestion

*Buvat J et al.*  
*J Sex Med 2013; 10: 245-284*
# Potential risk and safety information with T therapy (TT)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular disease</td>
<td>Neutral or beneficial effect</td>
</tr>
<tr>
<td>Lipid alterations</td>
<td>Neutral if physiologic replacement doses</td>
</tr>
<tr>
<td>Erythrocytosis</td>
<td>3 to 18% with transdermal administration</td>
</tr>
<tr>
<td></td>
<td>up to 44% with injection, ...</td>
</tr>
<tr>
<td>Fluid retention</td>
<td>Rarely of clinical significance</td>
</tr>
<tr>
<td>B.P.H.</td>
<td>Rarely of clinical significance</td>
</tr>
<tr>
<td>Prostate cancer</td>
<td>Controversial</td>
</tr>
<tr>
<td>Hepatotoxicity</td>
<td>Limited to oral administrations</td>
</tr>
<tr>
<td>Sleep apnea</td>
<td>infrequent</td>
</tr>
<tr>
<td>Gynecomastia</td>
<td>rare, usually reversible</td>
</tr>
<tr>
<td>Skin reactions</td>
<td>HIGH INCIDENCE with patch (up to 66%)</td>
</tr>
<tr>
<td></td>
<td>LOW INCIDENCE with gel (5%)</td>
</tr>
<tr>
<td></td>
<td>rare with injections</td>
</tr>
<tr>
<td>Testicular atrophy or infertility</td>
<td>Common in young men, <em>more with inj.</em></td>
</tr>
<tr>
<td></td>
<td>Reversible with cessation of treatment</td>
</tr>
</tbody>
</table>

*Adapted from Rhoden E.L. et al. N Engl J Med 2004; 350: 482-492*
Additional Risks of TT According to the 2008, ISA, ISSAM, EAU, EAA, and ASA Recommendations

- “Because the possible development of an adverse event during treatment (especially elevated hematocrit or prostate carcinoma) requires rapid discontinuation of testosterone substitution short-acting preparations may be preferred over long-acting depot-preparations in the initial treatment of patients with LOH”

- “17-α-alkylated testosterone androgen preparations such as 17-α-methyl testosterone are obsolete because of their potential for liver toxicity and should be no longer prescribed”

Conditions in which testosterone administration is associated with a high risk of adverse outcome and for which we recommend against using T
(According to the 2010 US Endocrine society guidelines)

**Very high risk of serious adverse outcomes**
- Metastatic prostate cancer
- Breast cancer

**Moderate to high risk of adverse outcomes**
- Unevaluated prostate nodule or induration
- PSA > 4 ng/ml (>3 ng/ml in individuals at high risk for prostate cancer, such as African Americans or men with first-degree relatives who have prostate cancer)
- Hematocrit >50%
- Severe lower urinary tract symptoms associated with benign prostatic hypertrophy as indicated by AUA/IPSS score >19
- Uncontrolled or poorly controlled congestive heart failure

_AUA/IPSS = American Urological Association / International Prostate Symptom Score_

# Seeking an Urological Consultation – Biological monitoring: alert criteria

**Relative**
- TT > 700 ng/dL < 50 yr
- More especially when between 50 to 65 years old

**Absolute (ask for urologic advice)**
- TT > 500 ng/dL in frailty or > 65y
- HCT > 52-54% (function lab value)
- PSA ↑
  - ≥ 1ng/mL in 12 months or >4ng/mL (abs. value)
  - During 1\textsuperscript{st} 24months
    - ≥ 0.75ng/mL in 12 months followed by additional increase in next 3-6 months
  - After 24 months >0.4ng/mL in 12 months followed by additional increase in next 3-6 months

---

*Buvat J et al.*
*J Sex Med 2013; 10: 245-284*
EVOLUTION OF Prostate Specific Antigen (PSA) by Duration of Treatment in Long-Term Study (Final)

MEAN PSA LEVELS in the PADAM study

Bouloux PM et al. Results presented at the EAU Congress, Italy 2008.
TRT clinical monitoring

- 3 to 6 months after starting the treatment
- 3 to 6 months later on
- After...each (6 to) 12 months

⇒ Clinical efficacy and tolerance evaluation

**Symptoms**
- After 6 months: if non response (stop or other causes)

**Clinical**
- Morning erection
- Sexual desire
- Energy
- Physical performance
- Waist circumference

**Tolerance**
- BP
- Breast
- Compliance
- DRE after 40 years

Buvat J et al.  
*J Sex Med* 2013; 10: 245-284
Why a « Physiological correction of T deficiency » with a gel in LOH?

- Contains 1% **body-identical** hormone
- Consistent and **constant** testosterone blood levels for a duration of 24 hours
- Lead to lesser decline in sperm count compared to injections
- Predictable bioavailability (87% of patients **always** remains in the physiological range)
- **Well tolerated** locally as well as systemically
- No skin irritation, easy tailoring of the treatment
- Dry quickly
- Odorless, colorless, not painful
- Can be interrupted **immediately** at any time

*Lunenfeld B et al. Aging Health 2009;5(2) :227-245*
Contra-indications of TT According to the 2008 /2015 ISA, ISSAM, EAU, EAA, and ASA Recommendations

- **Absolute Contra-indications**
  - Men suspected of or having carcinoma of the prostate or breast
  - [ant. of Sexual criminality, desire for fertility]

- **Relative Contra-indications**
  - Men should not be treated with testosterone if
    - High risk of developing prostate cancer
    - Severe symptoms of lower urinary tract obstruction
    - Significant erythrocytosis
    - Untreated severe congestive heart failure
    - Untreated obstructive sleep apnea