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Segretario Regionale SIAMS per la Lombardia
Key points

• Prevalence of Testosterone Deficiency (TD) increases with age in particular in pts with metabolic syndrome (about 50%) and sexual dysfunction

• Low Testosterone levels are associated with reduced longevity and quality of life:
  • increase of fatal cardiovascular events, obesity, sarcopenia, osteoporosis, depression, reduced sexual drive, erectile dysfunction and other chronic diseases

• Testosterone treatment in Metabolic Syndrome reduces waist circumference, BMI and insulin resistance

• Young men with TD should also be treated. In older men benefits and risks of testosterone replacement should be carefully assessed

• Nevertheless, even though these systemic complications, TD is underestimated and underthreated
MMAS (Massachusetts Male Aging Study)

Testosterone levels = good indicator of healthy

Feldman et Al., 2002
Lethality of major cardiovascular events and testosterone levels

Figure 2 Lethality of major adverse cardiovascular events (MACE) according to hypogonadal status. *$P < 0.001$, **$P < 0.0001$.  

Low testosterone predicts increased mortality and testosterone therapy improves survival in 587 men with type 2 diabetes (mean follow-up: 5.8 years).

Metabolic syndrome and hypogonadism

Muller et Al., 2005
**The BLAST study**

A 30-week double blind placebo controlled study of long-acting testosterone undecanoate versus placebo in men with type 2 diabetes

550 men identified from Diabetes register

488 consented and attended pre-screening visits

211 patients screened (mean age 62)
- 12 screen failures
- 1 AF, 10 raised PSA of which 9 were BPH and 1 new CaP – 1 withdrew consent

199 Randomised
- 97 randomised to TESTOSTERONE UNDECANOATE 1000 mg for 30 weeks
- 102 randomised to matching placebo for 30 weeks

190 Completed
- 4 SAEs – 3 treatment-unrelated deaths and 1 new CaP in PLACEBO arm – 5 withdrawn consent
- 106 entered 52-week open-label extension

HbA1c open-label: Poorly controlled patients (N=45)

HOMA-IR and serum INSULIN levels

HOMA-IR (mmol/l) \( p=0.22 \)

INSULIN levels (pmol/l) \( p=0.93 \)

- Baseline, 30 weeks, 82 weeks
- Nebido, Placebo, Open Label

Weight, BMI and waist circumference open-label study (N=106)

- Weight (kg) p=0.016
- BMI (kg/m²) p=0.019
- Waist (cm) p<0.001

BLAST open-label – IIEF (N=106)

IIEF: Erectile Function

\[ p=0.003 \]

IIEF: Intercourse Satisfaction

\[ p=0.005 \]
IIEF: Erectile Function
MEN TAKING PDE5 INHIBITORS (N=35)

Effects of 5-Year Treatment With Testosterone Undecanoate on Lower Urinary Tract Symptoms in Obese Men With Hypogonadism and Metabolic Syndrome

Davide Francomano, Alessandro Ilacqua, Roberto Bruzziches, Andrea Lenzi, and Antonio Aversa; Urology, 2013 in press

Variations in total International Prostate Symptom Score (IPSS)
Testosterone Therapy in Men With Prostate Cancer: Scientific and Ethical Considerations

Abraham Morgentaler*,†

From Men’s Health Boston and the Department of Urology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts

Conclusions: Although no controlled studies have been performed to date to document the safety of testosterone therapy in men with prostate cancer, the limited available evidence suggests that such treatment may not pose an undue risk of prostate cancer recurrence or progression.
IPASS - Nebid

IPASS: A Study on the Tolerability and Effectiveness of Injectable Testosterone Undecanoate for the Treatment of Male Hypogonadism in a Worldwide Sample of 1,438 Men

Michael Zitzmann, MD, PhD,* Andreas Matterm, PhD,† Jens Hanisch, PhD,‡ Louis Gooren, MD, PhD,¶ Hugh Jones, MD, PhD,§‖ and Mario Maggi, MD, PhD**


• N=1438 / 1493 patients included in safety population

• 1123 patients completed the study and received all 5 injections (78.1% continuation rate)

• In total, 6333 TU injections were administered

• Mean observation period: 9.2 ± 3.1 months
### PSA (ng/mL)

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>938</td>
<td>1.10</td>
<td>0.94</td>
</tr>
<tr>
<td>Visit 2</td>
<td>708</td>
<td>1.20</td>
<td>1.08</td>
</tr>
<tr>
<td>Visit 3</td>
<td>676</td>
<td>1.30</td>
<td>1.18</td>
</tr>
<tr>
<td>Visit 4</td>
<td>537</td>
<td>1.20</td>
<td>1.03</td>
</tr>
<tr>
<td>Visit 5</td>
<td>455</td>
<td>1.10</td>
<td>1.05</td>
</tr>
</tbody>
</table>

### Hematocrit (%)

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>843</td>
<td>42.8</td>
<td>6.56</td>
</tr>
<tr>
<td>Visit 2</td>
<td>725</td>
<td>44.0</td>
<td>5.83</td>
</tr>
<tr>
<td>Visit 3</td>
<td>684</td>
<td>44.7</td>
<td>6.05</td>
</tr>
<tr>
<td>Visit 4</td>
<td>534</td>
<td>44.7</td>
<td>6.18</td>
</tr>
<tr>
<td>Visit 5</td>
<td>474</td>
<td>44.5</td>
<td>6.12</td>
</tr>
</tbody>
</table>

PSA, prostate-specific antigen; SD, standard deviation

Testosterone Deficiency in Men (TD) / Late Onset Hypogonadism (LOH)

nevertheless, even though these systemic complications….
TD is underestimated and underthreatened!

Why?

• Underestimated: Symptoms and signs of late onset are even milder, unspecified and difficult to recognize

• Underthreatened: fear that testosterone replacement causes
  -prostate cancer or its progression  
    (in particular in men without severeTD)
  -Polycythemia

→ Long term systemic complications: increment of morbidity and mortality

→ Correct diagnosis, clinical assessment and treatment (International Guidelines)
SIAMS realised SOPHY (simple and updated diagnostic chart for TD) in order to make easier and promote the diagnosis of testicular deficiency, where is frequent but underestimated, as in the practice of diabetologist, internist, cardiologist, endocrinologist, urologist.

«EDUCATION»
### Symptoms of adult vs pre-puberal hypogonadism

Table 2  Symptoms, signs, and conditions indicative of Testosterone Deficiency [3,5,6,13,41].

<table>
<thead>
<tr>
<th>Most specific signs and symptoms</th>
<th>Less specific signs and symptoms</th>
<th>Most specific conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduced sexual desire and activity</td>
<td>Decreased energy, motivation, initiative</td>
<td>Type 2 diabetes mellitus</td>
</tr>
<tr>
<td>Decreased spontaneous erections</td>
<td>Delayed ejaculation</td>
<td>Metabolic syndrome</td>
</tr>
<tr>
<td>Erectile Dysfunction</td>
<td>Reduced muscle bulk and strength</td>
<td>Chronic obstructive lung disease, Obstructive Sleep Apnea Syndrome</td>
</tr>
<tr>
<td>Hot flushes, sweats</td>
<td>Diminished physical or work performance</td>
<td>End-stage renal disease, hemodialysis</td>
</tr>
<tr>
<td>Decreased testicle size</td>
<td>Mild anemia (normocytic, normochromic)</td>
<td>Osteoporosis</td>
</tr>
<tr>
<td>Loss of pubic hair, reduced requirement for shaving</td>
<td>Depressed mood, irritability</td>
<td>HIV- associated weight loss</td>
</tr>
<tr>
<td>Increased BMI, visceral obesity</td>
<td>Poor concentration and memory</td>
<td>History of infertility, cryptorchidism, pituitary disease, delayed puberty</td>
</tr>
<tr>
<td>Height loss, low trauma fractures, reduced BMD</td>
<td>Sleep disturbances, sleepiness</td>
<td>Treatment with opioids or glucocorticoids</td>
</tr>
</tbody>
</table>

*Wu FCW, 2010*
Threshold Levels for the Biochemical Diagnosis of TD

There are no generally accepted lower limits of normal TT (total testosterone). There is, however, general agreement that:

- **TT > 12 nmol/L (3.5 ng/mL or 350 ng/dL)** does not usually require substitution (EBMI1)

  - Based on the data of young hypogonadal men, men with **TT < 8 nmol/L (2.3 ng/mL or 230 ng/dL)** usually benefit from T treatment (EBMI1)

- Between these levels:
  - measuring FT (free testosterone) by equilibrium dialysis or calculating it from TT and SHBG levels* may be helpful in case of TT between 8 and 12 nmol/L. A lower limit of **225 pmol/L (65 pg/mL)** is accepted by many (EBMI3)

*www.issam.ch/freetesto.htm*
In the pilot phase of SOPHY:
5 centers, 47 physicians
From December 2013 available on SIAMS site

Coordinator: Alessandro Pizzocaro MD
Analysis of current situation

26 active physicians, 319 filled questionnaires, 272 analyzed

Diagnosis of Hypogonadism
128/272

New diagnosis 91/128

Correct diagnosis of hypogonadism 122/128
95.3%

Previous diagnosis 37/128
Exclusion of Hypogonadism

28.80% correct diagnosis
71.20% wrong diagnosis

Causes of error

<table>
<thead>
<tr>
<th>Cause</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total testosterone</td>
<td>32.5%</td>
</tr>
<tr>
<td>Borderline (NO SHBG)</td>
<td></td>
</tr>
<tr>
<td>NO testosterone assay in presence of symptoms</td>
<td>55%</td>
</tr>
<tr>
<td>Other</td>
<td>12.2%</td>
</tr>
</tbody>
</table>
Exclusion of Hypogonadism: wrong diagnosis

Specialist in Diabetology

- Patient: 71 years old, married, 2 sons, with hypertension, diabetes, cardiovascular disease, BPH, BPCO

<table>
<thead>
<tr>
<th>Patologie urologiche</th>
<th>terapie mediche in atto per qualsiasi patologia</th>
</tr>
</thead>
<tbody>
<tr>
<td>criptorchidismo</td>
<td>VELMETIA</td>
</tr>
<tr>
<td>NO</td>
<td>AMLODIPINA</td>
</tr>
<tr>
<td>carcinoma testicolare</td>
<td>AVODART</td>
</tr>
<tr>
<td>NO</td>
<td>CONGESCOR</td>
</tr>
<tr>
<td>carcinoma prostatico</td>
<td>COTAREG</td>
</tr>
<tr>
<td>NO</td>
<td>COUMADIN</td>
</tr>
<tr>
<td>iperplasia prostatica</td>
<td>ONBREZ</td>
</tr>
<tr>
<td>benigna</td>
<td>SPIRIVA UROREC</td>
</tr>
<tr>
<td>NO</td>
<td>terapia per disfunzione erettile (PDE5I)</td>
</tr>
<tr>
<td>disturbi della minzione</td>
<td>Vardenafil</td>
</tr>
<tr>
<td>(Lower Urinary Tract Symptoms, LUTS)</td>
<td></td>
</tr>
<tr>
<td><strong>Hypogonadism Symptoms</strong></td>
<td></td>
</tr>
<tr>
<td>---------------------------</td>
<td></td>
</tr>
<tr>
<td>&quot;ha avuto più o meno desiderio di fare l’amore nel corso degli ultimi tre mesi?&quot;</td>
<td>Sì</td>
</tr>
<tr>
<td>desiderio sessuale ipoattivo: specifiche</td>
<td></td>
</tr>
<tr>
<td>sì, ma meno rispetto a prima</td>
<td></td>
</tr>
<tr>
<td>&quot;Le è mai capitato di svegliarsi con un’erezione negli ultimi 3 mesi?&quot;</td>
<td>Sì</td>
</tr>
<tr>
<td>Riduzione del numero delle erezioni notturna e mattutina: specifiche</td>
<td></td>
</tr>
<tr>
<td>sì, ma meno frequenti di prima</td>
<td></td>
</tr>
<tr>
<td>Disfunzione erettile (nel raggiungimento e/o nel mantenimento dell’erezione negli ultimi 3 mesi)</td>
<td>Sì</td>
</tr>
<tr>
<td>disfunzione erettile dettaglio</td>
<td>disfunzione erettile mantenimento</td>
</tr>
<tr>
<td>difetto nel mantenimento</td>
<td>qualche volta &lt; 25% dei casi</td>
</tr>
<tr>
<td>numero dei rapporti sessuali nel periodo (es: 3/mese)</td>
<td></td>
</tr>
<tr>
<td>3/Mese</td>
<td></td>
</tr>
<tr>
<td>&quot;ha notato una riduzione (volume) della quantità di sperma (etaculato) negli ultimi 3 mesi?&quot;</td>
<td>Sì, un po’ ridotto</td>
</tr>
<tr>
<td>&quot;Le capita di venire troppo alla svelta?&quot;</td>
<td>Sì</td>
</tr>
<tr>
<td>eiaculazione precoce (EP)</td>
<td></td>
</tr>
<tr>
<td>da quanto tempo è presente?</td>
<td></td>
</tr>
<tr>
<td>&quot;ha difficoltà a raggiungere l’orgasmo o di venire troppo tardi o addirittura di non venire?&quot;</td>
<td>NO</td>
</tr>
<tr>
<td>ridotta frequenza rasatura della barba</td>
<td>NO</td>
</tr>
<tr>
<td>astenia</td>
<td>Sì</td>
</tr>
<tr>
<td>tristezza</td>
<td>NO</td>
</tr>
<tr>
<td>ridotta capacità a compiere esercizi fisici intensi</td>
<td>Sì</td>
</tr>
<tr>
<td>ridotta capacità di concentrazione</td>
<td>Sì</td>
</tr>
</tbody>
</table>
Clinical diagnosis and laboratory analysis

mammelle dettaglio
normali

volume
aumentato

noduli
NO

superficie
regolare

consistenza
aumentata

dolore
NO

testosterone totale
2.35
NG/ML

glicemia basale
unità di misura
110
mg/dl

insulina basale

HbA1c (emoglobina glicosata)
unità di misura
6.8
%

colesterol totale
unità di misura
235
mg/dl

HDL
unità di misura
57
mg/dl

trigliceridi
unità di misura
112
mg/dl

Nuova diagnosi di ipogonadismo
NO
Hypogonadism Treatment Percentage in diagnosed cases

- Treated: 80.80%
- Not treated: 16.5%
- Not treated (other Specialist): 7.0%
Hypogonadism Not Treated

Specialist in Endocrinology

- Patient: 45 years old, married, no sons, familiar with T2 diabetes mellitus and cardiovascular disease; 1 cigar; < 2 drink; no sport

Altro: Dislipidemia

Terapia: Eutirox mcg/die, Omeprazolo mg, Vytorin.
Hypogonadism Symptoms

"ha avuto più o meno desiderio di fare l’amore nel corso degli ultimi tre mesi?"  Si

desiderio sessuale ipoattivo: specifiche

"le è mai capitato di svegliarsi con un’erezione negli ultimi 3 mesi?"  Si

Riduzione del numero delle erezioni notturne e mattutine: specifiche

Disfunzione erettile (nel raggiungimento e/o nel mantenimento dell’erezione negli ultimi 3 mesi)  Si

disfunzione erettile dettaglio disfunzione erettile raggiungimento

• difetto nel raggiungimento
• difetto nel mantenimento disfunzione erettile mantenimento

numero dei rapporti sessuali nel periodo (es: 3/mese)

"ha notato una riduzione (volume) della quantità di sperma (eiaculato) negli ultimi 3 mesi?"  Si, molto ridotto

Diagnosis

Nuova diagnosi di ipogonadismo  Si

Viene instaurata/modificata la terapia?  NO

Il paziente viene inviato a ulteriore specialista?  NO
Formulation

- Inj. Long-acting (Nebid) 20.4%
- Inj. Short-acting (Testoenant, Testoviron e Sustanon) 27.6%
- Gel (Tostrex, Testogel, Testim) 36.8%
- Oral (Andriol) 2%
- Not Specified 7.1%
- Gonadotropin 6.1%
- Not specified 7.1%
Thanks for your attention!

Alessandro Pizzocaro