MYTHS AND CONTROVERSIES IN HYPOGONADISM TREATMENT OF AGING MALES

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(Abstract): Low T is an independent risk factor for metabolic syndrome (MetS) and type 2 diabetes mellitus (T2DM) development; patients with these clinical conditions should be screened for hypogonadism. Testosterone replacement therapy (TRT) ameliorates libido, improves bone mass, improves insulin resistance, reduces fat mass and increases lean body mass with no change in body weight. There are no evidences that testosterone therapy increases the risk of prostate cancer but it is certain that testosterone stimulates growth of metastatic prostate cancer. TRT has an anti-arrhythmic and a vasodilator effect, independent of the nitric oxide effect. Patients with heart failure have low levels of testosterone, and TRT improves exercise capacity. Men with low testosterone have risk for premature death. Cardiovascular adverse effects of testosterone therapy are under discussion. We need large prospective placebo-controlled randomized trials to determine definitively the cardiovascular risks of TRT. Keywords: MALE HYPOGONADISM, TESTOSTERONE REPLACEMENT THERAPY, DIABETES MELLITUS, METABOLIC SYNDROME, CARDIOVASCULAR RISK, MORTALITY.

Late onset hypogonadism (LOH) is a clinical and biochemical syndrome associated with advancing age and characterized by symptoms and a deficiency in serum testosterone level; it may cause a significant deterioration in quality of life and functional alterations of multiple organs (1,2). In the Massachusetts Male Aging Study (MMAS) after the age of 40 the average age-related reduction in total testosterone is 0.8% per year, whereas free testosterone declines by 1.7-2.8% per year; the prevalence of sytomatic hypogonadism is between 6-12% (3). In European Male Aging Study (EMAS) the prevalence of hypogonadism is 2.1% and increase with age from 0.1% for men 40-49 years of age to 5.1% for those 70-79 years (4). The odds of having low testosterone levels is 2.4 higher for obese men, 2.1 times higher for men with diabetes, 1.58 times higher for men with hypertension, and 1.5 times higher for those with dyslipidemia or chronic obstructive pulmonary disease (1,5).

Clinically, the syndrome is characterized by:
- reduce sexual desire, low libido, erectile dysfunction, reduction of spontaneous erections
• breast tenderness, gynecomastia
• corporeal hairiness reduction, reducing the frequency of shaving
• mood changes with reduced intellectual activity, cognitive functions, spatial orientation ability and memory
• fatigue, depression and irritability, decreased mood
• sleep disorders, hot flushes, sweating
• decrease muscle mass and muscle strength
• increased body fat mass, increased BMI
• osteopenia / osteoporosis and increased risk of fracture
• mild anemia (Hb and Ht normal values for women) (6, 7).

The MMAS has shown that a lot of comorbid conditions are strongly associated with declining testosterone levels; in these cases it is suggested measurement of testosterone level:
• metabolic syndrome
• obesity
• hyperlipidemia
• hypertension
• elevated fasting glucose and serum insulin elevated C reactive-protein
• diabetes mellitus type 2
• chronic obstructive pulmonary disease
• cardiovascular disease (including aortic atherosclerosis)
• inflammatory arthritic disease
• HIV-associated weight loss
• end stage chronic kidney disease
• low trauma fracture
• sellar mass, radiation in the sellar region
• chronic use of glucocorticoids and opioids
• hemochromatosis (2, 8, 9).

The diagnosis is made by subnormal values of total testosterone and the combination of characteristic symptoms.

Testosterone circulates bounded to Sex Hormone Binding Globulin (SeHBG) (68%), loosely bound to albumin (30%) and only 0.5-3% is free. Total testosterone levels may vary depending on the SeHBG value.

**Total Testosterone** is determined in the morning, 8-11 AM, by RIA, immunometric methods or ideal liquid chromatography tandem mass spectrometry (LC-MS), 2 determinations at intervals of at least 1 month (10). The dosage of **free testosterone** is expensive; the only method validated is by equilibrium dialysis. **Bioavailable Testosterone** (free plus the loosely bound to albumin) is determined by ammonium sulphate precipitation method, or is calculated from total testosterone, SeHBG and albumine level.

SeHBG - binds testosterone with higher affinity than estrogen. The values are increased in elderly, liver cirrhosis, hyperthyroidism, anticonvulsant therapy, estrogen, HIV and decreased in moderate obesity, hypothyroidism, nephrotic syndrome, acromegaly, corticosteroid use, androgen treatment, progesterone (10, 11).

It is not recommended a population screening for androgen deficiency (2); in certain circumstances (see above), there is a high prevalence of low testosterone levels and it is suggested measurement of serum testosterone (tab. I).

Testosterone treatment is recommended:
- at patients with typical clinical signs of androgen deficiency and biological confirmation
- for a limited time for patients with HIV infection, low testosterone and weight loss to increase and maintain lean mass (3-6 months)
- short chronic glucocorticoid therapy (prednisone equivalent 5-7.5mg/day) due to inhibition of gonadotropic axis (2,12).
Myths and controversies in hypogonadism treatment of aging males

TABLE I

<table>
<thead>
<tr>
<th>Society</th>
<th>Serum testosterone values</th>
</tr>
</thead>
<tbody>
<tr>
<td>EAA, ISA, ISSAM</td>
<td>&lt;3.4 ng/ml &lt;340 ng/dl &lt;12 nmol/l (mild)</td>
</tr>
<tr>
<td>EAU, ASA, ISSM</td>
<td>&lt;2.31 ng/ml &lt;231 ng/dl &lt;8 nmol/l (severe)</td>
</tr>
<tr>
<td>ES</td>
<td>&lt;3.0 ng/ml &lt;300 ng/dl &lt;10.4 nmol/l</td>
</tr>
<tr>
<td>AACE</td>
<td>&lt;2.0 ng/ml &lt;200 ng/dl 7 nmol/l</td>
</tr>
</tbody>
</table>


The goal of treatment (2, 11) is to safely restore testosterone to normal physiological levels, thereby ameliorating symptoms associated with TD and improving patient health and well being.

Options for testosterone therapy include oral preparations (2-3 doses per day), buccal agents, injections (at 2-3 weeks or at 12-14 weeks), transdermal systems (patches, gels, solutions) or subcutaneous pallets (tab. II).

TABLE II

<table>
<thead>
<tr>
<th>Testosterone</th>
<th>Administration/Dose</th>
<th>Adverse events/ Disadvantages</th>
<th>Monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Testosterone enantat/ cipionat</td>
<td>75-100 mg / 7 days or 150-200 mg / 14-21 days i. m.</td>
<td>wide fluctuations in serum testosterone levels</td>
<td>testosterone level at the middle interval between 2 injection</td>
</tr>
<tr>
<td>Testosterone undecanoat inj.</td>
<td>1000 mg i. m every 12-14 weeks</td>
<td>an enhancement at dose administration</td>
<td>immediately until the next injection</td>
</tr>
<tr>
<td>Testosterone non- scrotal patches</td>
<td>5-10 mg/ day</td>
<td>local irritation</td>
<td>at 3-12 hours after application</td>
</tr>
<tr>
<td>Testosterone gel</td>
<td>50-100mg/day</td>
<td>transfer during close contact</td>
<td>anytime (&gt; 7 days after initiation)</td>
</tr>
<tr>
<td>Buccal testosterone</td>
<td>30mg /day</td>
<td>taste changes</td>
<td>immediately</td>
</tr>
<tr>
<td>Oral Testosterone Undecanoat</td>
<td>40-80mg x 2-3/day, during meals</td>
<td>digestive effects</td>
<td>at 3-5 hours after administration</td>
</tr>
<tr>
<td>Testosterone implants</td>
<td>4-6 implants of 200 mg, every 4-6 month</td>
<td>risk of extrusion or infection</td>
<td>at 3-5 hours after administration</td>
</tr>
</tbody>
</table>

Monitoring of testosterone treatment is recommended:
- first, at three months from therapy initiation, and then annually;
- determination of hematocrit (Ht); Ht > 52%-54% during the treatment is an indication of stopping the administration of testosterone, assessment of hypoxia and sleep-apnea, and after normalization of Ht restarting with lower doses of testosterone (2,9).

- BMD by DXA is repeated every 12-24 months in hypogonadal men with osteoporosis or fragility fractures;
- digital rectal examination and PSA checking are performed before treatment, at 3 months, and then in accordance with guideline for prostate cancer screening depending on age; urological evaluation is necessary if:
  - PSA > 4 ng / ml
- PSA increase of more than 1.4 ng/ml within any 12 month period of testosterone treatment
- PSA velocity of more than 0.4 ng/ml/year, using PSA level after 6 month of testosterone administration as reference (only if PSA data are available for at least 2 years)
- Score for prostatic symptoms > 19 (AUA-American Urology Association or IPSS-International Prostate Symptoms Score - Europe)

Positive effects of testosterone administration are translated by improving mood, well-being and erectile function, or erectile response at phosphodiesterase 5 inhibitors administration, increasing of muscle mass and strength, especially in the upper limbs, decreasing of abdominal fat, increasing of bone mass. Short-acting testosterone preparations are preferred because it can be immediately interrupted if side effects occur.

Testosterone therapy in ageing men with hypogonadism is indicated only if the positive effects outweigh the risks, and after patient information about treatment risks and benefits.

Conditions in which testosterone administration is associated with increased risk of adverse effects:

- very high risk of serious adverse outcomes in metastatic prostate cancer and breast cancer
- moderate to high risk of adverse outcomes in unevaluated prostate nodule or indurations, or unexplained elevations of PSA (>4 ng/ml), Ht >50%, severe lower urinary tract symptoms, uncontrolled or poorly controlled congestive heart failure (class III, IV), severe, not treated sleep apnea (1,2).

In young patients, the goal testosterone concentration is midlevel of normal; at ageing patients, the goal is lower level of normal. There is no basis for dose escalations in pursuit of greater efficacy, and the practice may increase the risk of side effects. The vitality, energy and libido are ameliorated in the first 3 months of treatment, but the effect on body composition is evident latter, and is related directly with the testosterone level.

Adverse events for which there is evidence of association with testosterone administration:

- male pattern balding, acne
- gynecomastia - may exist before treatment
- induction or worsening of obstructive sleep apnoea
- worsening of Benign Prostate Hyperplasia (BPH)
- detection of subclinical prostate cancer, growth of metastatic prostate cancer;
- increased hematocrit
- reduced sperm production and infertility
- cardiovascular events (1, 2, 10).

EFFECTS OF LOW TESTOSTERONE AT VARIOUS ORGANS AND SYSTEMS; POSITIVE AND NEGATIVE EFFECTS OF TRT IN AGING MALES

Sexual function

Low testosterone reduces libido but the effect on erectile function is less obvious; erectile dysfunction is associated with low testosterone only among men with high luteinizing hormone (LH) levels. There are evidences suggesting therapeutic synergism with combined use of testosterone and phosphodiesterase-5 (PDE) inhibitors in hypogonadal or borderline eugonadal men (9, 13, 14).

Prostate cancer and BPH

There is no conclusive evidence that testosterone therapy increases the risk of prostate cancer. It is certain that testosterone stimulates growth and worsening of
symptoms in patients with advanced or metastatic prostate cancer. On the other hand, there are studies indicating that the aggressiveness of prostate cancer is higher in patients with low testosterone. For this reason, it is recommended at least one digital prostate exam and PSA evaluation before initiation of androgen therapy.

Also an IPSS > 21 or > 19 for AUA lower urinary tract symptoms (LUTS) are relative contraindication to androgen therapy. Contraindication is not maintained after treatment of prostatic pathology (14, 15). Rectal digital examination and PSA checking are indicated every 3-6 months at the beginning of treatment, and then annually.

**Cognition, mood and energy**

Some studies found benefits in improving spatial ability, verbal fluency, and working memory in elderly men. In a meta-analysis reviewing the effects on depression, testosterone therapy was found to have beneficial effects on mood and depression (10, 16).

**Bone metabolism, bone mass and fractures**

The prevalence of osteoporosis in hypogonadal males is 2-fold increased compared with eugonadal males. Testosterone administration improves bone mass after aromatization to estradiol: spinal BMD increased by 8%. Effects on femoral neck are inconclusive. No fractures studies have been reported. Aging hypogonadism is associated also with vitamin D deficiency but the clinical significance of this relationship has to be investigated (10, 13, 17).

**Body composition, muscle strength and risk of falling**

Interventional studies indicate an improvement in body composition with an increase in lean mass and decrease in fat mass after administration of testosterone in hypogonadal patients; it seems that the risk of falling by improving mobility is also reduced by administration of testosterone, although the mechanisms involved are not clear (10, 13).

**Obesity**

In MMAS study, average Body Mass Index (BMI) was 28.5 to 31.5 kg/m² for eugonadals and respective hypogonadals. 20-64% of obese men have low total and free testosterone levels, and low levels are associated with insulin resistance, metabolic syndrome and type 2 diabetes. The exact mechanism of the interrelationship between obesity and low testosterone is related to reduced abdominal lipolysis in case of androgenic deficit, increased visceral fat determining increase aromatase production, with increasing testosterone to oestrogen conversion and pituitary inhibition. Androgen replacement therapy reduces fat mass and increases lean body mass, with no overall changes in body weight (9, 10, 13, 18).

**Lipid metabolism**

Hypogonadal men have increased levels of total cholesterol and triglycerides (15). TRT decreases total cholesterol in men with lower testosterone levels, with no effect on triglycerides level (19); the effect of TRT in elderly men on LDL-C and HDL-C is controversial. Supraphysiological testosterone levels induce an increase in LDL-C and decrease in HDL-C levels, and increase the risk of cardiovascular disease.

**Metabolic Syndrome and Diabetes Mellitus**

Epidemiological evidence from several longitudinal population studies shows that low testosterone (T) is an independent risk factor for the development of both MetS and T2DM. Interaction between insulin resistance, visceral adiposity, and hypo-
gonadism is not sufficiently elucidated, but seems related to the increased production of aromatase, leptin levels and inflammatory cytokines (15, 18). Veterans of U.S. with prostate cancer and anti-androgenic therapy have a higher incidence of type 2 diabetes, myocardial infarction, stroke and sudden cardiac death, and acute antiandrogen-therapy reduces insulin sensitivity and strongly impairs glycemic control of men with T2DM. Prospective studies have shown that men with higher T levels had a 42% lower risk of T2DM. In men with type 2 diabetes, metabolic syndrome and hypogonadism, testosterone therapy improves insulin resistance, as measured by HOMA-IR and reduces HbA1 by approximately 0.7% by 18 months.

Thus, a vicious circle ensues in which MetS suppresses T biosynthesis and conversely, reduced T concentrations predispose and contribute to the onset of development of MetS and in turn obesity (15, 18, 20).

Based on this epidemiological evidence, current guidelines suggest that patients with clinical conditions associated with insulin resistance (obesity, T2DM, and MetS) should be screened for hypogonadism.

**TESTOSTERONE THERAPY AND CARDIOVASCULAR SYSTEM**

**Antiarrhythmic effect**

Testosterone has an antiarrhythmic effect due to the observation that a low testosterone causes QTc prolongation (increased incidence of ventricular arrhythmias), reversible by testosterone administration. This effect is explained by increasing expression of Kv1.5 K+ channels and L calcium channels (15, 21).

**Testosterone and atherosclerosis**

It exist an inverse correlation between testosterone concentration and thickness of the intima (as marker for preclinical atherosclerosis): on the one hand, the metabolic effects, the increasing of the local inflammatory response (IL6, hCRP, TNF, IL-1B), apoptosis and lowering vascular smooth muscle cell stability of a low testosterone are cardiovascular risk factors, and on the other hand atherosclerosis determines low testicle perfusion and low testosterone secretion (15, 20).

Another effect of testosterone is as vascular vasodilator, independent of nitric oxide, possibly by inhibiting L-type and T-type calcium channels. (20,21). In the same way, men with lower levels of endogenous testosterone are more prone to develop coronary artery disease (CAD) during their lifetime, and it exists a correlation between the severity of CAD and the degree of testosterone deficiency (20,22). TRT is positively associated with a significant increase in treadmill test duration and time to 1mm ST segment depression in men with stable coronary artery disease. TRT improves the angina threshold (14, 20) and reduces the infarct size comparative with that in hypogonadal subjects not treated (21). Controversy, there are studies (in rats) that show that exogenous testosterone exacerbate atherosclerosis and it exist a proapoptotic effect of testosterone (21, 23). In his study, Glueck has demonstrated that men with coagulability problems (factor V Leiden mutation or elevated homocysteine) have an increased risk for thromboembolism at 3 months after androgen therapy initiation (24). Prospective epidemiological studies are needed to analyze in detail the association between coronary heart disease and endogenous bioavailable testosterone (20, 23).

**Heart failure**

A key feature of congestive heart failure (CHF) is metabolic shift toward catabolism,
with activation of neuroendocrine and inflammatory pathways. The result is worsening of exercise intolerance. Studies show that patients with heart failure have low levels of total and free testosterone, and that with worsening severity of cardiac failure, there is a significant stepwise decrease in testosterone concentration (20, 25). Furthermore, it was hypothesized that the only predictor of the degree of deterioration of exercise capacity (using peak VO2, peak-VO2 pulse) is the magnitude of testosterone levels reduction. This means that the association between serum testosterone and aerobic exercise capacity is independent of the severity of heart failure, the use of beta-blockers or chronotropic response to exercise (20). Testosterone therapy in cardiac failure improves exercise capacity by 0.5 DS, not by effect on left ventricular ejection fraction, but by a peripheral direct mechanism on the skeletal muscles, by causing a shift toward more type I muscle fibers in patients with CHF. Low testosterone in cardiac failure patients correlates negatively with exercise capacity and is associated with a worse prognosis and higher mortality, and TRT is associated with a significant improvement in exercise capacity (20, 25).

**MORTALITY**

Men with low testosterone are at risk of premature death; testosterone value below 8 mmol / l increases mortality three times, and five times the cancers risk (28), and a decreased testosterone with 2.1 DS is associated with an increased risk of cardiovascular mortality by 25% (20). Low testosterone is associated with increased mortality in diabetic patients, and TRT improves the survival (13, 20, 23, 26, 27, 28).

Cardiovascular risk and androgen therapy is a very controversial topic because an optimal level of testosterone is a biomarker for survival, but the androgen therapy may increases the risk of nonfatal MI. There are a lot of studies that find no increase in the cardiovascular events in case of testosterone replacement therapy, but pharmaceuticals companies support many of them. Studies that had alert about the cardiovascular risk are also critical because no one had as endpoint the cardiovascular risk and the TRT, most studies involved have small cohorts with a small number of events, the study population was old (over 70 years), with cardiac problems, the doses of testosterone were very high (100mg/day) (29), or the alternative study drug was an PDE inhibitor that provide cardiovascular-protective effect (30, 31), or the impact of symptoms as an indication for TRT prescribing was not analyzed because is well-known that the presence of erectile dysfunction is an independent cardiovascular risk factor (increase the incidence of CV events with more than 50%)(30, 31, 32).

This apparent discordance between low testosterone as cardiovascular risk factor and the potential cardiovascular risk of testosterone replacement therapy could be explained by Corrona’s concept of “low testosterone syndrome” - an adaptive response in order to be more resilient to a pathological condition (cardiovascular frailty: T2DM, CVD); the low testosterone is only a marker for poor health, for saving energy (less physical and sexual activity) and to protect species (low fertility) (14).

Another explanation for these discrepancies between low levels of testosterone as cardiovascular risk factor and the cardiovascular risk in case of TRT, could be that endogenous testosterone is beneficial, but exogenous testosterone and its metabolites could be harmful, the degree of testosterone deficiency is not similar in late onset hypogonadism (LOH) versus Klinefelter
syndrome, or induced hypogonadism in prostate cancer, auto medication and self increasing doses (14).

If we want to respond to this debate: Is low testosterone level in CVD a positive consequence of the body trying to decrease unnecessary energy (and in this situation the treatment might be deleterious for overall and cardiovascular health) or it represents a pathophysiological factor in the CVD (in this situation the treatment is recommended), we need large prospective placebo-controlled randomized trials such as the Women's Health Initiative to determine definitively the cardiovascular risks of TRT. Until this, physicians and patients should have a conversation about the risks and benefits of using testosterone, especially in patients who have pre-existing heart disease (32, 33).

In conclusion, LOH is frequently co morbid with almost all severe and chronic diseases; clinicians have to look for hypogonadism in men with MetS, T2DM or CV disease, and conversely to look for metabolic and CV co morbidities when hypogonadism is found. TRT is able to improve central obesity (subjects with MetS), glycometabolic control and insulin resistance, ameliorate exercise capacity and survival. Appropriately prescribed testosterone is undoubtedly beneficial, but caution needs to be taken in certain situations, as the associated health/benefits of TRT to outweigh the potential increased risk of cardiovascular-related events.

REFERENCES


