

## Is there an andropause, better known as Testosterone Deficiency Syndrome, and if so, what tissues are affected and how?

### Fertility, androgen production and sensitivity, osteoporosis and sexual function in aging men

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The isolation and synthesis of the testosterone molecule more than 70 years ago led to major discoveries in urology related to the fields of gender differentiation, fertility, sexual function and, of course, prostate gland development and health. Despite the many years of study, a great deal of controversy still exists regarding the diagnosis, treatment and monitoring of Testosterone Deficiency Syndrome (TDS). Figure 1 summarizes these issues and the Endocrine Society has provided a reliable guideline on this subject.

nation as well as a basic battery of tests to confirm that an insufficient level of testosterone in plasma exists. Common manifestations of testosterone deficiency include tiredness, fatigue, irritability, sexual difficulties, sleep disturbances and hot flashes. None of the symptoms can be diagnostic on its own, as other conditions such as depression and thyroid dysfunction can present a similar clinical picture. Standardized questionnaires exist to facilitate the initial assessment. However, they lack specificity to be used as a diagnostic tool. Physical signs of TDS include truncal obesity, sarcopenia and osteoporosis. Hypogonadism has been increasingly linked to the manifestations of the metabolic syndrome (MetS), a combination of medical disorders that increase the risk of developing cardiovascular disease and diabetes.

A biochemical assessment is mandatory in the diagnostic process for TDS. At the very minimum, it requires a total plasma testosterone determination. Borderline values call for a repeat determination. A low testosterone level in the presence of elevated gonadotropins is diagnostic. Although hyperprolactinemia is a rare condition, it is known to cause secondary hypogonadism. Thus measurement of serum prolactin is advisable if testosterone level is low. Occasionally, a clear clinical picture of TDS is not supported by the laboratory evaluation. Since the measurement of testosterone in peripheral blood is an inaccurate reflection of tissue levels of the hormone, it has been recommended, in this situation, to offer a 3-month trial of testosterone replacement therapy. Interpretation of laboratory results is important. Total testosterone measurement is adequate in the vast majority of cases and it is a reliable and consistent technique that is widely available. The measurement of free testosterone is not recommended because only a handful of laboratories perform this test properly. By measuring sex-hormone binding globulin and total testosterone, a simple calculation can provide the so-called calculated free testosterone or calculated bioavailable testosterone, both of which are considered a reliable reflection of androgenicity.

### Treatment

Upon confirmation of TDS and in the absence of contraindications, very few reasons are there to withhold testosterone therapy (TT). There are, currently, many choices available each one with its own advantages and drawbacks.

1. *Oral:* Testosterone undecanoate is safe but is required to be taken with a substantial amount of fat to permit adequate absorption by the gut. When this condition is met, adequate levels of serum testosterone can be reached.

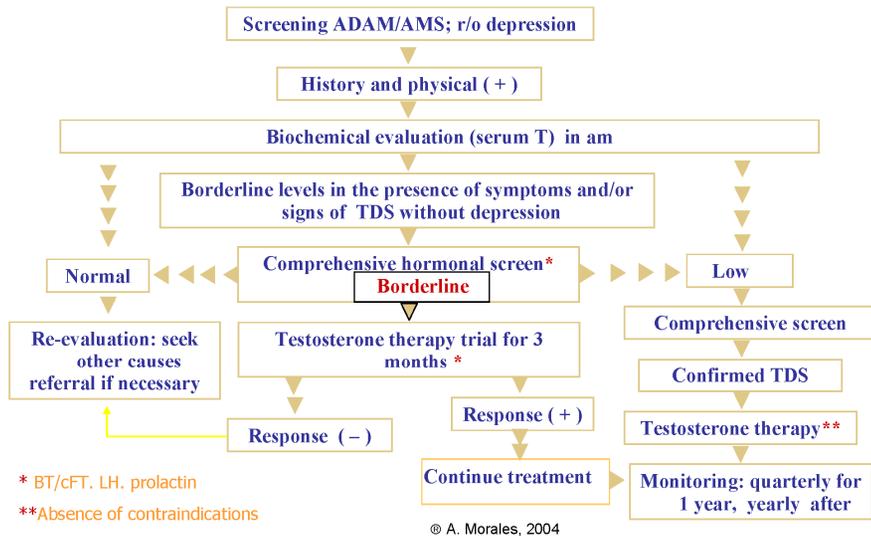


FIG. 1. Diagnostic algorithm for Testosterone Deficiency Syndrome (TDS)

### Diagnosis

The clinical diagnosis involves an adequate history and physical exami-

2. **Transdermals:** Non-scrotal patches are currently rarely used in North America because of the high incidence of skin reactions of variable severity. New patches are currently available in Europe. The manufacturers appear to have been able to circumvent the skin problems without interfering with the medication transfer.
3. **Injectables:** They constitute the earliest form of testosterone administration. Depot preparations requiring injection every 2-3 weeks are still very popular because of the low cost and the certainty of absorption. A new injectable formulation of testosterone undecanoate is available in several continents (excluding North America, at the time of writing). It requires administration every 12 weeks which is a definitive advantage.
4. **Transdermal gels:** These preparations have become increasingly popular due to the ease of administration, availability and efficacy.
5. **Non testosterone alternatives:** Under special circumstances (i.e. secondary / hypogonadotropic) TDS, a man may be a candidate for gonadotropins administration. There are also herbal, so called “phyto-androgens” of unproven efficacy. The use of dehydroepiandrosterone (DHEA) has been popular for decades but its efficacy remains highly controversial.

A few facts are worth remembering while diagnosing, treating and monitoring men with TDS:

1. The diagnosis requires a combination of clinical features and clinical low serum levels of testosterone. Not uncommonly, patients fall into a gray zone of clear symptoms but questionable biochemistry.
2. Determination of total serum testosterone is usually sufficient. Assays for free or bioavailable testosterone are properly done by just a handful of laboratories; therefore these assays are not recommended for routine clinical practice.
3. In the presence of symptoms of TDS (and absence of co-morbidities such as depression, hypothyroidism) and biochemistry results not confirming the clinical impression, we first recommended a 3-month therapeutic trial.
4. There is no evidence whatsoever that testosterone administration promotes the development of prostate cancer. But, the growth of a sub-clinical cancer might be enhanced by testosterone therapy.
5. Competent monitoring should take place every 3 months (some argue that every 6 months is sufficient) for the first year. If the patient is responding and there are no significant adverse effects, monitoring is continued on a yearly basis for the duration of treatment, which is, normally, for life.

6. Competent monitoring consist of, at least:
  - Assessment of clinical response and testosterone dose-adjustment if needed.
  - Evaluation of any possible adverse effects.
  - Physical assessment, including digital rectal examination (DRE).
  - Biochemical assessment which includes: total testosterone levels, hemoglobin and hematocrit; total, LDH and LDL cholesterol; PSA;
  - Determination of gonadotropins, other hormones (prolactin) and liver function tests are needed under special circumstances only.

## Summary

TDS occurs for a variety of reasons but aging is, probably, the most common reason for these men to seek advice. The understanding of the syndrome, its diagnosis, treatment and monitoring are not particularly complicated but demand interest and serious commitment.

## Suggested reading

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