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Servicio Navarro de Salud / Osasunbidea
Plaza de la Paz, s/n - 31002 Pamplona
T 848429047 - F 848429010
farmacia.atprimaria@cfnavarra.es

abstract

Objective: to carry out a critical appraisal of the Testosterone Deficit Syndrome (TDS), also known as low testosterone or T-low, its diagnosis and management. **Materials and methods:** a bibliographic search was carried out in the TRIP database and PubMed with the following key words: "testosterone deficiency", "late-onset hypogonadism", "male andropause" and "androgen deficiency in aging males" filtered by the type of study (clinical practice guidelines, systematic reviews, meta-analyses or clinical trials). Information on consumption and sales was obtained from invoiced prescriptions in Navarre from 2001 upto 2011. **Results:** many of the signs and symptoms that define this syndrome overlap with those produced by other health problems or even physiological conditions. Self diagnostic questionnaires present scarce predictive value and are not recommended for screening. Nor is there certainty about which biochemical parameter is clinically appropriate where even the interpersonal variability is high. The cut off points to determine the normality of the testosterone levels vary depending on the guidelines employed. Testosterone supplements do not modify total weight, nor do they improve muscular strength. There is no evidence of their effects on bone fractures and there is a very discrete increase in bone density. Evidence is lacking on whether there is a significant improvement on sex life. Far from reducing cardiovascular risk, as initially postulated, there are studies that actually show an increase. Other associated risks of this therapy include prostate morbidity, increase in hematocrit count, liquid retention, sterility and feminization. **Conclusions:** testosterone therapy in the management of TDS is not justified because there is no clear benefit in the relevant primary endpoints and there are alarming results on the possible risks. Increasing consumption responds to the success of awareness raising campaigns. TDS is a clear example of disease mongering. **Key words:** Testosterone. Hypogonadism. Testosterone Deficiency Syndrome. Andropause. Disease mongering.

Medicalization of aging and the testosterone deficiency syndrome

JUAN GÉRVAS
Family Physician. CESCA group, Madrid, Spain

ENRIQUE GAVILÁN
Family Physician, Montehermoso Primary Care Centre, Cáceres, Spain

JAVIER GORRICHO
Drug Prescribing Service. Navarre Health Service, Spain

Introduction

The Brown-Séquard method of treatment consists of replacing the same organ (or an extract) when missing or failing, for example, insulin supplements when the pancreas fails. At the age of 72, the same Charles Brown Sequárd (1817-94) employed his own method by administering via subcutaneous injection the "elixir of life," an extract from the testicles of animals. This elixir became well known as Brown Sequárd attributed powers to it that reputedly increased strength, controlled constipation and increased sexual drive and strenght in urinary flow.

The vasectomy of Sigmund Freud also became famous in the 1920´s. Freud believed in the sperm theory of aging which attributed this process to the "loss" of sperm. As in the case of Brown Sequárd, there were thousands of convinced imitators, doctors, scientists and lay people.

In both cases masculine aging was linked to sexuality in a biunivocal relationship that could be reversed through a simple intervention. Time has elapsed, but the same idea still prevails, now only there are supplements of testosterone.

Leydig cells in the testicle produce testosterone, although this hormone is also synthesized in the ovary and the adrenal cortex. Testosterone circulates in the blood stream bound to albumin and also as free plasma testosterone. Inside cells it is metabolized to dehydroandrosterone, its most active form, thanks to the action of the alpha-reductase enzyme. It acts by binding to nucleus receptors and produces androgenic and anabolic effects. Estradiol is produced as a result of catabolic activity. Testosterone is segregated by the masculine fetus from the eighth week after conception (plasma levels of 250 ng/dL) and as a result internal and external genital organs develop. During childhood secretion is minimal, and at puberty, males masculinize when testosterone is segregated in great quantities (plasma levels of 500 and 700 ng/dL) through the stimulus of the luteinizing hormone (LH), following a circadian rhythm which reaches peak levels at 8 am. Pituitary secretion of LH depends on the pulses from the gonad releasing hormones of the hypothalamus. Over the years, the secretion of testosterone falls, approximately 1% per annum, upto levels of 300 ng/dL in elderly males.[1]

Classical hypogonadism is a documented disease, either provoked by disorders such as the Klinefelter syndrome or testicular injury, in which there is evidence of hypothalamic-pituitary-adrenal axis often with severe health consequences. In these cases, the testosterone supplementation is justified.

However over the last few years it has been proposed that the simple fact of having testosterone below the normal levels, which occurs with the passage of time, provokes a constellation of disorders in men that can be reverted by the administration of this hormone. This is what is now known as the Testosterone Deficiency Syndrome (TDS). In this paper, we will carry out a critical appraisal of TDS, including its diagnosis and management.

The controversial diagnosis of TDS

As commented, TDS is characterised by biochemical tests (low testosterone values) and a series of disorders, theoretically due to low levels of the hormone.

Clinical characteristics

The signs and symptoms that characterise TDS are vague. Among them we find some *sexually related disorders* (loss of pubic hair, erectile dysfunction), physiological disorders (fatigue, fat deposits, reduction of muscular mass), and psychological alterations (discouragement, asthenia, sleep-related problems). Many of these overlap with problems produced by other processes such as osteoarthritis, depression, senile fragility, and malnutrition. Some others are associated with the normal process of aging.

To diagnose TDS there are various proposed questionnaires including these unspecific symptoms. The most employed and reproduced screening tool in awareness campaigns is the ADAM *(Androgen Deficiency in Aging Males)*. Of scarce sensitivity and low positive predictive value, it should not replace the measurement of testosterone levels and does not serve as a surrogate endpoint of TDS.[2] Nor do other more complex questionnaires such as the *Aging Male Symptoms* (AMS) predict the hormone level.[3,4]

Only 6 of the 32 items included in these questionnaires are related to low testosterone levels: three regarding sexuality (reduction in sexual desire, less frequent matinal erections, and erectile dysfunction); two psychological aspects (sadness and fatigue) and one physical aspect (inability to carry out vigorous activity.[5] On the other hand, treatment with testosterone in patients with TDS does not correlate with changes in the responses to the questionnaires.[6] As a consequence its use is scarce, if any.

Biochemical diagnosis

There is no certainty on what parameter is clinically appropiate, although the determination of total testosterone levels is generally accepted (results of which are highly variable depending on the laboratory technique, individual and time of the day). Nor is there consensus on what defines "normal" and pathological levels. Some medical associations propose a cut-off point for baseline total testosterone

of 300 ng/dL (10.4 nmol/L)[7] while others increase it to 350 ng/dL (12 nmol/L).[8] This discrepancy explains in part the disparity in published data on the prevalence of TDS, between 2 and 39% in males over 40 years.

Strictly speaking, the diagnosis of TDS should include the presence of well defined signs and symptoms, and low levels of free plasma testosterone in the absence of secondary causes that may justify both criteria, in addition to a favourable response to treatment.[9] The fact that a large part of the improvement is attributed to placebo raises further doubts on the diagnostic and treatment process involved in TDS.

Efficacy of testosterone supplementation in patients with TDS

Testosterone has been employed for multiple purposes based variably on scientific grounds. Among them, the management of symptoms related to hypogonadism, the improvement in athletic ability of sportsmen and the use as a "miracle" product against aging. Its use in TDS aims at improving quality of life and preventing associated morbidity, acknowledging that testostoerone can increase muscular strength, reducing bone fractures, improving sexual functions and the quality of life, reducing in addition cardiovascular risk. But is there any truth behind these beliefs?

Weight and body composition

In randomised clinical trials testosterone was shown to slightly modify the proportion of body fat/non-fat with no change in the total weight.[10] So, fatty mass is reduced and non-fatty mass is increased. These effects are not persistent and disappear in 6 months after withdrawing treatment.[11]

Muscular strength and mobility

The discrete increase in the proportion of non fatty mass in the organism does not reflect an evident improvement in muscular strength. Only a modest improvement in the extension of the knee and hand prension has been objectively shown, both outcomes with doubtful clinical significance. No differences have been shown in either physical function and mobility tests.[12,13]

Bone mineral density and fractures

There is no clinical trial studying the effects of testosterone on the incidence of bone fractures. There are two meta-analyses[10,14] in which an increase of 8% in bone mineral density in lumbar spine was shown after treatment with intramuscular testosterone (no statistically significant differences for the transdermal route). None of the testosterone presentations produced improvements on mineral density at the hip.

Testosterone Deficiency Syndrome is not a disease

Sexual function

Two meta-analyses[15,16] were carried out to evaluate the efficacy of testosterone supplements on the sexual function in men. These present inconsistent results between different outcomes in the same studies, the results are also divergent when comparing the studies, and a high risk of publication bias was observed. The authors conclude that there is no clear evidence of its efficacy[15] and more randomised clincial trials are necessary.[16]

Later on, a clinical trial comparing testosterone with placebo[17] was published in which 237 patients (aged 60 to 80 years) undertook treament with testosterone undecanoate 40 mg/12h for 6 months to improve sexual function. No evidence of efficacy was found. Nor is there any evidence that treatment improves quality of life related to sex life.

Cardiovascular risk

Some authors[18] theorized on the possible benefit of preserving the "integrity of cardiovascular health" of the elderly. In the clinical trials this theory was not confirmed but rather the contrary was found. In one meta analysis[19] on testosterone supplements and cardiovascular safety, a trend towards increasing cardiovascular events in the group under testosterone was seen, though differences did not reach statistical significance, OR 1.82 (95%CI, 0.8-4.2).

A later trial was early stopped when the group under testosterone treatment achieved a higher incidence of cardiovascular events. This study, financed by the NIH in the USA, was carried out on 209 men (average age, 74 years) with numerous risk factors (diabetes, hypertension, obesity). The adjusted OR was 5.8 (95%CI, 2.0-16.8) for cardiovascular events and 7.2 (95%CI, 0.9-59.7) for atherothrombotic events.

Using testosterone for TDS bears risks and does not offer any benefit

Quality of life

No differences in the quality of life of the patients, measured through different scales including specific tests such as ADAM and AMS, have been shown.

For all the above mentioned, testosterone in TDS has not shown any clear benefit with regard to significant variables for patients.

Safety of TDS treatment

Long-term safety of TDS treatment is unknown as the only data available proceeds from short-term low-quality studies. In many cases it implies lifelong treatment but the trials last 6 months only.

In one meta-analysis[21] an increase in hematocrit and hemoglobin was observed as an adverse effect. Later on, a published clinical trial[20] already mentioned was discontinued due to adverse cardiovascular effects. The treatment with testosterone is also related to liquid retention, worsening of heart failure, gynecomastia, sterility and feminization.

In another meta-analysis,[22] an increase in adverse prostate events, OR = 1.78 (95%CI, 1.07-2.95) associated with the use of testosterone in eldery patients was found. In the Spanish Summary of Product Characteristics it is warned that "androgens may accelerate the progression of subclinical prostatic cancer and benign prostatic hyperplasia". However, there is no published clinical trial that helps determine the increase in risk of prostate cancer associated with this treatment.

In the *Women's Health Initiative*[23] trial on hormone replacement therapy (HRT) the danger of assuming that HRT could reduce cardiovascular risk was made evident. In fact, it was observed that there was an increase in cardiovascular risk related to HRT.

Likewise, evidence-based knowledge on the balance between the benefits and harm of the use of testosterone in the managment of TDS depends on carrying out well designed randomised clinical trials of sufficient size and adequate duration.

According to the available information, treatment with testosterone is not justified in patients with TDS as there are no consistent results with respect to the benefit in clinically relevant endpoints but rather alarming results with regard to the possible adverse effects.

Consequently, it should be understood that the Spanish Summary of Product Characteristics reports of drugs with testosterone restrict their indication to male hypogonadism when the clinical picture and biochemical tests confirm testosterone deficiency. It is insisted that treatment should not be used for unspecific symptoms of hypogonadism, when testosterone deficiency has not been shown, or when other causes of these symptoms have not been ruled out.

Promotion of the diagnosis and treatment of TDS

The FDA´s approval in 2000 of the first testosterone in gel form was associated with the extensive use of the treatment, which up to then was restricted to concrete situations. This more comfortable method of application was added to persistent direct marketing campaigns and disease awareness incitiatives of T-low (low testosterone) focussed on the general public and professionals.

In the USA the propaganda incited middle aged males to recover their masculinity lost over time. In a highly competitive society this fits in perfectly as a message that reverts "decrepitude", as if males were "reparable" machinery, the stronger the better, with the promise of an incredible personal, work and sex life in the elderly age.[24]

In Spain, the propaganda arrived later and has been focussed on the relationship between TDS and cardiovascular and metabolic disorders. The typical image of the affected person with TDS is very different from that in the English speaking world and reflects social and cultural differences. In Spain, and in mediterranean countries, the target audience of marketing campaigns is the ordinary 50 year old male, with a slightly overweight belly due to excess food, or beer, and without realizing, it could present "an important underlying cardiovascular problem and the risk of death".[25] It is custom to appeal for "men's right to health".[26] The campaign promotes the creation of a "prevention culture" in order to initiate the medicalization process. Active participation of health professionals serves as an alibi to achieve greater social legitimacy. An exemplary campaign is the public awareness program carried out by BAYER "Tenemos una edad" *(We are getting older).*[27]

The promotion directed towards physicians is carried out at opinion leader meetings, courses, conferences, scientific journal papers and specialized literature. In some occasions direct mention of the brands qualifies these activities as purely commercial.[28]

Finally, the objective is reached and sales revenues of testosterone preparations grow with no epidemiogical base. In 2001, sales in the USA were well over 1600 million dollars.[29] In Australia every new modification made to the testosterone presentation is accompanied by an increase in prescriptions reaching a four-fold increase between 1992 and 2010.[30] This phenomenon has also be witnessed in Spain (figures 1 and 2).

TDS as an example of disease mongering

The Brown Sequard method is routinely employed in cases such as insulin-dependent diabetes and hypothyroidism. In the same way, the administration of testosterone allows for optimum levels to be reached in disorders such as Klinefelter syndrome (the most frequent cause of hypogonadism). Beyond the reasonable use of testosterone, the extension of

Figure 1. Evolution of the consumption of testosterone in Navarre in DHD.

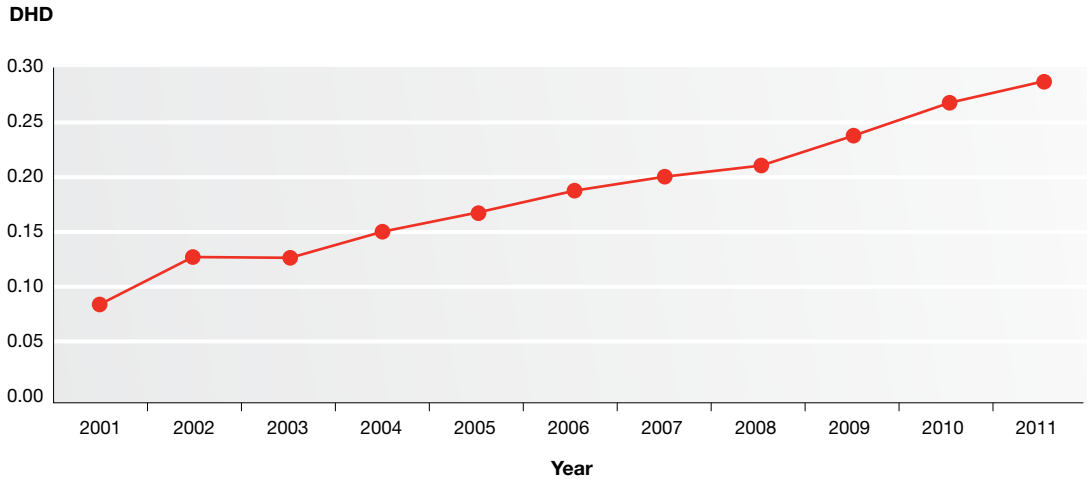
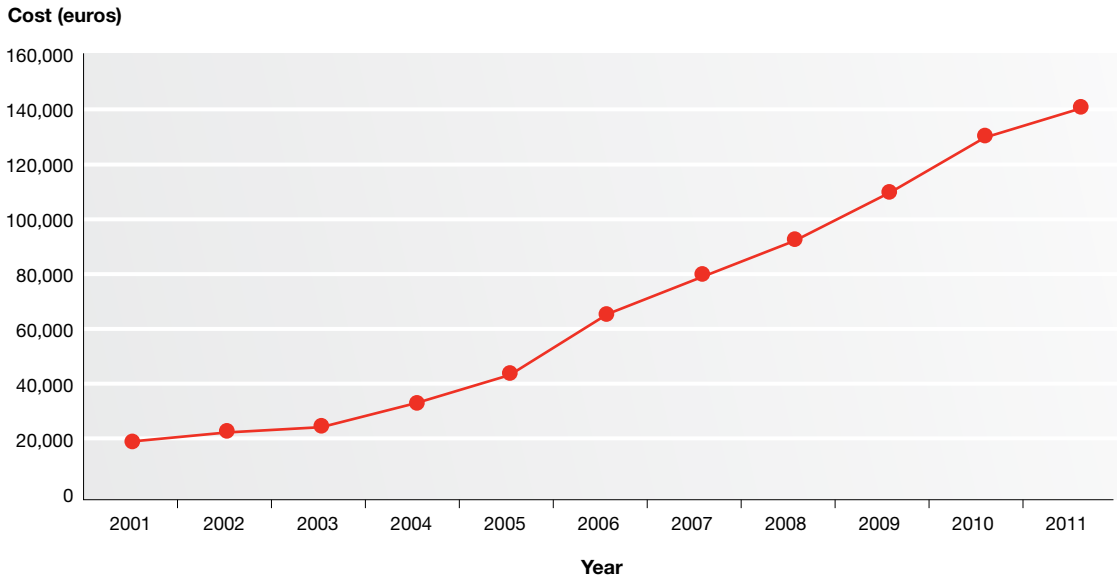


Figure 2. Evolution of the consumption of testosterone in Navarra in cost terms (€).



Evolution of the consumption of testosterone in Navarre over the last 11 years

In figure 1 the unit of measure is DHD (daily defined dose per 1000 inhabitants) and an increase of 237% was observed during this period. In figure 2, an increment of 620% in sales (euros) was observed in this period. The slope of both graphs increases its inclination in 2004. It is important to recall that from this year, the first presentations of testosterone in gel form were made available in the Spanish market: Testogel (2004, Bayer), Testim (2005, Ferring) and Itnogen (2007, Prostrakan). In 2008, two other products were added in the form of transdermal patches: Intrinsa (2008, Warner Chilcott) and Testopatch (2008, Pierre Fabre).

The proposed diagnostic methods should not be employed and only serve to medicalize a natural process

the indications of testosterone is promoted to other entities such as TDS which is considered to be like hypogonadism.

The crucial point is the "appropiation" of the definition of "normality" to convert a natural and healthy process related to aging to a "pathological" condition. The slow and gradual decrease of testosterone levels is associated with deterioration and a promise is made to revert the symptoms through hormone replacement therapy.[31]

Experts determine through biometry the "normality" of aging, in such a way that males are "expropriated" of living healthily according to their age and the singularities of being human. Thus a number of guidelines, agreements and "consensus" emerge that define TDS according to responses from questionnaires and low levels of testosterone, to be considered in males over 45 years of age.[32] No doubt, there is mention of situations where TDS is most likely to occur (hypertension, metabolic syndrome, diabetes, obesity, use of opioids, COPD and osteoporosis), up to the point of even demanding routine screening of patients by citing prevalences of nearly 40%.[33,34] No benefit whatsoever has been shown with either this determination, or with the mechanisms proposed to justify treatment, yet doubts are maintained and the issue is taken even further by proposing testosterone use in heart failure[35] for example, and/or associating TDS and obesity to higher cardiovascular mortality.[36]

During the process, family physicians are implicated as they bear the highest social credibility and new knowledge is spread among the public through expert interventions and awareness campaigns. The idea is simple: TDS can be diagnosed and treated, in both mature and elderly men. Eternal youth is promised alluding to the loss or decrease in sexual potency and the unsatisfied partner is encouraged to consider TDS[37]. Sex is reduced to the genitals, virility to erection, and the process of aging to a loss in testosterone. Andropause is associated with menopause and men are encouraged to imitate women's behaviour with respect to turning to "preventive" medical care.

Moreover, other relevant issues are ignored such as the lack of sensitivity in the questionnaires, the artificial determination of "normal" levels, scarce response and reversal of symptoms after treatment and related adverse effects.

On the whole this represents a pure exercise of disease mongering[38-41] which achieves the increase in use of testosterone with uncertain benefits but sure injury to patients (and evident improvements for stakeholders). There is even room to help patients decide by explaining to them the meaning of quartenary prevention.[42]

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Conclusions

TDS is a clear example of how there is an attempt to medicalize a physiological process with no benefit for people.

TDS comprehends signs and symptoms that overlap with those present in other health problems or even may be physiological.

Treatment with testosterone has not shown any clinically relevant benefit in these patients.

Testosterone supplements have been associated with important adverse effects.

Long-term safety of the drug is still unknown.

Propaganda regarding TDS in Spain has been focussed on its supposed (false) favourable action on cardiovascular problems.

The hard experience resulting from hormone replacement therapy in women should serve as a warning to avoid committing the error of transforming a hormonal change to disease.

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Servicio Navarro de Salud / Osasunbidea
Plaza de la Paz, s/n
31002 Pamplona
T 848429047
F 848429010

E-mail
farmacia.atprimaria@cfnavarra.es

Web site
www.dtb.navarra.es