



Testosterone Deficiency: A Common, Unrecognised Syndrome?

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Article info

Keywords:

Erectile dysfunction
 Hypogonadism
 Metabolic syndrome
 Prostate cancer
 Testosterone deficiency
 Testosterone treatment

Abstract

Context: Testosterone deficiency syndrome (TDS) is highly prevalent in ageing men. Associated symptoms may significantly impair quality of life and may affect the function of multiple organ systems. In addition, TDS may have an impact on life expectancy. Although still the subject of debate, testosterone administration may hold promise in symptomatic hypogonadal men.

Objective: To present an overview of current data on TDS and treatment of hypogonadal patients with testosterone.

Evidence acquisition: This manuscript is based on presentations given at a satellite symposium on TDS held at the 2nd World Congress on Controversies in Urology (CURy) in Lisbon, Portugal. Data were retrieved from recent review papers and original papers on TDS, metabolic syndrome, and erectile dysfunction (ED).

Evidence synthesis: Preliminary data of the Transversal European Survey on Testosterone deficiency Diagnosis (TESTo-Dia) demonstrated that physicians need more information and education on TDS. Although there is no clear-cut testosterone threshold at which overall symptoms appear, testosterone deficiency can be associated with severe symptoms and conditions such as cardiovascular disease, diabetes, metabolic syndrome, and ED. Consequently, appropriate treatment of hypogonadal men is highly warranted. There are compelling data showing that testosterone administration does not increase the risk of prostate cancer. Moreover, treatment of testosterone deficiency appears to have a neuroprotective role. Based on these data, physicians may not withhold testosterone treatment from hypogonadal patients. Current treatment options include testosterone administration via gels, patches, capsules, or implants. A new transdermal-matrix patch appears to be safe and effective in hypogonadal men.

Conclusions: Although long-term randomised controlled trials are needed, treatment with testosterone in selected symptomatic hypogonadal men may have a beneficial effect on symptoms and/or prevention of several age-related disorders.

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1. Introduction

According to recommendations of the International Society of Andrology (ISA), the International Society for the Study of Aging Male (ISSAM), the European Association of Urology (EAU), the European Academy of Andrology (EAA), and the American Society of Andrology (ASA), testosterone deficiency syndrome (TDS) is defined as a clinical and biochemical syndrome associated with advancing age that is characterised by symptoms (eg, low libido, increased fat mass, decreased muscle mass, loss of concentration, erectile dysfunction (ED), depression, and decreased bone mineral density) and by a deficiency in serum testosterone levels. There is general agreement that total testosterone levels >12 nmol/l (346 ng/dl) do not require testosterone substitution. Similarly, based on data from younger men, there is consensus that serum total testosterone levels <8 nmol/l (231 ng/dl) require substitution [1,2]. Testosterone deficiency is currently underdiagnosed, may result in reduced quality of life, and can adversely affect the function of multiple organ systems. The overall prevalence of TDS varies from 6% to 9.5% in community-dwelling men aged 40–70 yr and rises to 15–30% in diabetic or obese men [3,4]. Demographic data clearly demonstrate the increasing percentage of older men with testosterone deficiency, supporting the concept that serum testosterone levels decline gradually and progressively with age. There is a significant percentage of men aged >60 yr with testosterone levels below the lower limits for young adult men. A cross-sectional cohort study among 434 consecutive male patients aged 50–86 yr demonstrated that the prevalence of psychosomatic symptoms and metabolic risk factors accumulated with decreasing testosterone levels (<15 nmol/l [433 ng/dl]). A clear-cut threshold for testosterone deficiency was not found [5]. Another cross-sectional survey of 3200 community-dwelling men aged 40–79 yr from a prospective cohort study in eight European countries demonstrated the age-dependent decline of testosterone levels, which is augmented by high body fat and underlying medical conditions [6]. In addition, low serum testosterone levels (<8.7 nmol/l [250 ng/dl]) appear to be associated with increased mortality in male veterans aged >40 yr [7]. In the Hypogonadism in Males (HIM) study, among men aged at least 45 yr presenting to primary care practices in the United States, the prevalence of hypogonadism (defined as total testosterone <10.5 nmol/l [300 ng/dl]) was estimated to be 38.7% [8]. Medical conditions including obesity, diabetes, hypertension, rheumatoid arthritis, and osteoporosis occurred significantly more frequently among these hypogonadal men. More recently, Laughlin et al [9] demonstrated that older men with total testosterone levels <8.4 nmol/l (241 ng/dl) had a 40% increased risk of death compared with men with higher testosterone levels (>12.9 nmol/l [370 ng/dl]) during an average follow-up of 11.8 yr, independent of multiple risk factors and preexisting health conditions. Important questions include whether these hypogonadal men may benefit from testosterone supplementation and whether or not this therapy is associated with risks. Recent studies showed short-term

advantages of testosterone therapy in hypogonadal men. Long-term data of testosterone treatment are limited and require further investigation. Additionally, the long-term effects of testosterone treatment on the prostate and the cardiovascular system need to be studied. Consequently, testosterone deficiency has become an interesting but debatable topic throughout the world [1,2].

2. Evidence acquisition

This paper was based on presentations given at a satellite symposium on TDS that was held during the 2nd World Congress on Controversies in Urology (CURy) on 6 February 2009 in Lisbon, Portugal. Data were retrieved from the Transversal European Survey on Testosterone deficiency Diagnosis (TESTo-Dia) and from recent review papers and original papers on TDS, metabolic syndrome, and ED.

3. Evidence synthesis

3.1. Opinion survey on diagnosis of testosterone deficiency syndrome

An estimation of the current knowledge of professional practices is necessary for defining educational needs on TDS. The preliminary results of the TESTo-Dia were presented during the symposium. For this opinion survey, a postal questionnaire was sent to all urologists, to all endocrinologists, and to 9000 general practitioners throughout Spain, Italy, Germany, and France. Items of the questionnaire included practitioner's medical profile, volume of practice (ie, number of patients with testosterone deficiency per practice), symptoms or signs suggestive of TDS, biochemical diagnosis, treatment, and perceived side-effects. Unfortunately, at the time of the symposium, the response rate was very low and varied from 0.53% to 9.00%. To date, the number of patients suffering from testosterone deficiency who are followed by urologists appears to be different among the European countries. The volume of practice seems to be much more balanced in Spain and Germany than in Italy and France. This difference cannot be explained by a difference in medical education. Furthermore, in this survey, no consensus seems to be reached among European urologists regarding the cut-off value of serum total testosterone between 200 ng/dl and 350 ng/dl (6.9 nmol/l and 12.1 nmol/l, respectively) (Fig. 1) and the use of testosterone fractions for the diagnosis of biochemical testosterone deficiency. Therefore, standardisation of diagnostic criteria would be relevant. With regard to testosterone supplementation, the majority of urologists seem to prefer modern preparations, but prostate safety is still a major concern.

3.2. Why should we have to treat testosterone deficiency syndrome?

3.2.1. Testosterone and metabolic syndrome

The metabolic syndrome (Table 1) [10] is a cluster of comorbidities and is associated with an increased cardiovascular risk. It is often found in viscerally obese

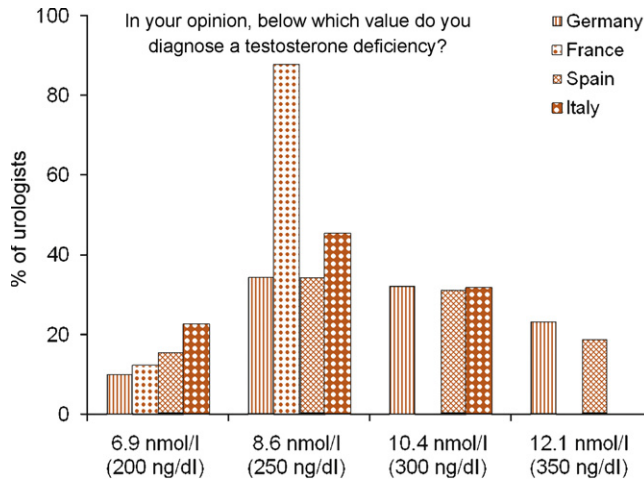


Fig. 1 – Preliminary results of the Transversal European Survey on Testosterone deficiency Diagnosis (TESTo-Dia) of the opinion among European urologists regarding the cut-off value of serum total testosterone for the diagnosis of biochemical testosterone deficiency.

patients, and insulin resistance plays a key role in its pathogenesis. Several new features, including increased inflammatory mediators, have been added to the definition of metabolic syndrome over time and are probably related to both insulin resistance and obesity [11].

Evidence suggests that many components of the metabolic syndrome such as insulin resistance and obesity are also present in hypogonadal men. A study conducted in Norway showed that low total testosterone levels in men are associated with a higher waist circumference, despite relatively low overall obesity [12]. Consequently, waist circumference might be a first indication of low testosterone levels in men. Haidar et al [13] showed that androgen deprivation therapy may have negative effects on glycaemic control in men with insulin-dependent diabetes and may aggravate the biochemical risk profile of cardiovascular disease to which diabetics are predisposed. All of these observations are in agreement with the emerging role of low levels of testosterone in metabolic syndrome and insulin resistance [14]. Moreover, Singh et al [15] observed that testosterone induces myogenesis and inhibits adipogenesis in mouse pluripotent stem cells, providing an explanation for the reciprocal effects of testosterone on muscle and fat in men. Thus, there seem to be vicious circles in the relationships among testosterone, visceral fat, inflammation, and insulin resistance (Fig. 2). Changing lifestyle by increasing physical activity and caloric restriction combined with testosterone

substitution may improve insulin resistance and cardiovascular problems. According to a meta-analysis of middle-aged and ageing men, testosterone administration seems to reduce fat mass and increase muscle mass [16]. In addition, Kapoor et al [17] demonstrated that testosterone administration improves insulin resistance and glycaemic control in hypogonadal men with type 2 diabetes. Similarly, Mårin et al [18] showed a beneficial effect of testosterone therapy on diastolic blood pressure and insulin resistance in abdominally obese men. Larger long-term studies, however, are needed to evaluate the advantages of testosterone treatment in hypogonadal men with diabetes or metabolic syndrome.

3.2.2. Testosterone and erectile dysfunction

Many age-related clinical features, including ED, are closely associated with testosterone deficiency [19]. Because many men are reluctant to discuss ED with their physicians, the condition remains underdiagnosed. Approximately 70% of ED cases have organic origins, with the major risk factors being diabetes, hypercholesterolaemia, smoking, and hypertension. The introduction of phosphodiesterase type 5 inhibitors (PDE5-Is) for the treatment of ED revolutionised the management of the condition. Some patients, however, fail to respond to PDE5-I monotherapy [20].

A close relationship has been demonstrated between testosterone and ED. Many studies have confirmed that testosterone is important in modulating the regulation of erectile function [20–24]. Animal studies showed that testosterone deprivation reduced the intracavernosal pressure. Furthermore, testosterone deprivation affected erectile function and induced structural alterations in the corpus cavernosum, with veno-occlusive dysfunction [20,21,24]. Therefore, testosterone treatment may be a valuable option in the management of hypogonadal men with ED. The combination of testosterone and PDE5-Is seems to be beneficial in men with ED and low testosterone levels [22,25,26]. Blute et al [27] demonstrated that testosterone therapy can convert more than half of those men who failed to respond to PDE5-Is into PDE5-I responders. Yet it is still unclear whether hypogonadal men should be treated initially with PDE5-Is, with testosterone, or with a combination of both.

3.3. Is there a link between testosterone replacement therapy and prostate cancer?

The number of prostate cancer (PCa) survivors who are symptomatically hypogonadal and who request treatment

Table 1 – Profile of a man defined as having metabolic syndrome, according to the new International Diabetes Federation (IDF) worldwide definition [10]

A waist circumference ≥ 94 cm plus at least two of the following four factors:	
Raised triglyceride levels	≥ 150 mg/dl or specific treatment for this lipid abnormality
Reduced HDL cholesterol	< 40 mg/dl or specific treatment for this lipid abnormality
Raised blood pressure	Systolic blood pressure ≥ 130 mm Hg and/or diastolic blood pressure ≥ 85 mm Hg or antihypertensive treatment
Raised fasting plasma glucose	≥ 100 mg/dl or previously diagnosed type 2 diabetes

HDL = high-density lipoprotein.

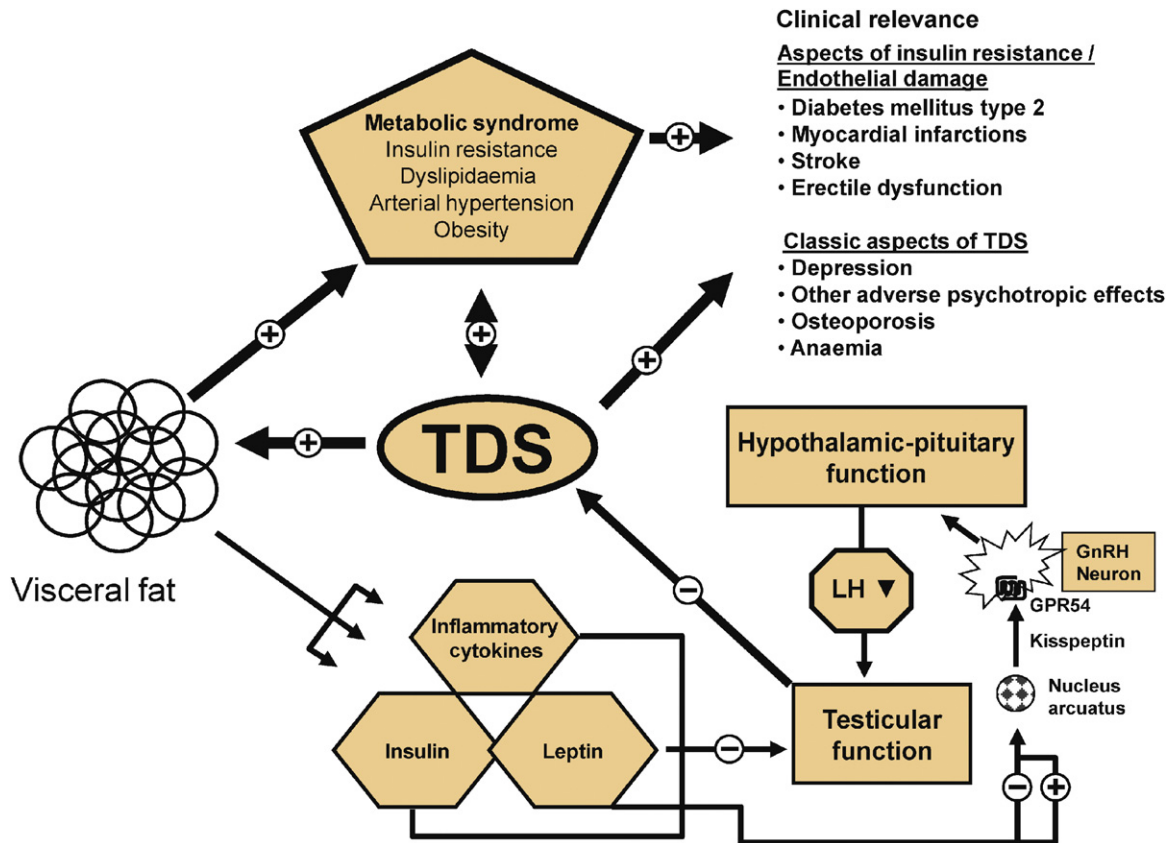


Fig. 2 – Vicious circles among visceral fat, metabolic syndrome, and testicular function. TDS = testosterone deficiency syndrome; LH = luteinising hormone.

is increasing. In accordance with preliminary results presented during the symposium, a recent international survey indicated that the fear of inducing PCa is the most frequently cited concern of physicians regarding the use of testosterone therapy [28]. Based on historical experiences [29,30], it was believed that testosterone administration caused PCa growth and could induce rapid progression. More recent data, however, have shown no apparent increase in PCa rates after testosterone administration in normal men or in men who are at increased risk of PCa. Moreover, in multiple longitudinal studies, no relationship between PCa risk and serum testosterone levels and no reduced risk of PCa in men with low testosterone were observed. The apparent paradox in which castration causes PCa to regress but higher testosterone fails to cause PCa to grow is resolved by a saturation model. In this model, maximal stimulation of PCa is reached at relatively low levels of testosterone [31–33]. More provocatively, findings based on in vitro cell lines suggest that testosterone may have a beneficial effect on PCa by promoting a less aggressive phenotype via the androgen receptor [34,35].

3.4. New perspectives on testosterone treatment

Based on the data cited above, testosterone seems to be a complex regulator of functional and structural homeostasis in multiple organ systems. Moreover, some evidence supports the hypothesis that testosterone may act protec-

tively in neuroinflammatory and neurodegenerative disorders such as Alzheimer's disease, multiple sclerosis, and depression [36,37]. As a result, testosterone therapy in hypogonadal men may hold therapeutic promise for treatment of symptoms or conditions and/or prevention of age-related disorders with neuronal injury.

Currently available preparations of testosterone (ie, intramuscular, subdermal, transdermal, oral, and buccal) appear to be safe and effective, with each formulation having its own drawbacks and advantages [1,2]. Transdermal testosterone gels and patches have been shown to normalise serum testosterone levels and reverse the symptoms of testosterone deficiency in hypogonadal men. Acceptance of the closed-system testosterone patches, however, has been limited by skin irritation or lack of adherence [38]. According to a randomised, multi-centre, open-label, controlled, 1-yr study, a new testosterone-in-adhesive-matrix patch (two patches of 60 cm² every 48 h; Testopatch[®], Pierre Fabre, Toulouse, France) appears to restore the physiological amount of testosterone produced per day (4.8 mg) corresponding to plasma levels >3 ng/ml in 85% of hypogonadal men. In the extension study (4 yr of follow-up; Pierre Fabre Medicament, unpublished data), the percentage of patients with total testosterone levels within the physiological range was maintained. In addition, this new formulation allowed smooth and regular plasma levels, improved clinical symptoms, and avoided adhesive failure, skin intolerance, and cross contamination [39,40].

4. Conclusions

Although the response rate of an opinion survey on testosterone deficiency was low, preliminary results indicate that physicians require more information and education on diagnosing testosterone deficiency and the safety of testosterone treatment. Increasing evidence suggests a relationship between testosterone deficiency and a number of conditions such as (visceral) obesity, metabolic syndrome, diabetes, ED, and even Alzheimer's disease. Consequently, men presenting with metabolic syndrome, diabetes, or ED should be screened for TDS. In addition, appropriate treatment of hypogonadal men is warranted. Testosterone administration should favour formulations that are capable of maintaining stable physiological levels of testosterone over time (eg, Testopatch[®]). Long-term randomised, placebo-controlled trials, however, are needed to determine whether testosterone treatment can safely extend the quality of life of older men with testosterone deficiency.

Conflicts of interest

Claude C. Schulman is speaker/advisor for Astellas, Novartis, Pierre Fabre Medicament, OM Pharma, and Eli Lilly. Ferdinando Fusco is speaker/advisor for Eli Lilly, Pierre Fabre Medicament, and GlaxoSmithKline. Antonio Martin Morales is speaker/advisor for Pierre Fabre Medicament, Prostrakan, Bayer Schering Pharma, Eli Lilly, Pfizer, and Janssen-Cilag. Jacques Tostain is speaker/advisor for Pierre Fabre Medicament. Michael Zitzmann has given lectures in symposia sponsored by Solvay, BayerScheringPharma, and Pierre Fabre. Pedro Vendeira is speaker for Eli Lilly, Pierre Fabre Medicament, and Janssen-Cilag.

Funding support

None.

Acknowledgments

The authors are grateful to Ismar Healthcare NV for assistance in writing this manuscript.

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