Issues in testosterone management: terminology, safety, genetics

Keywords
Testosterone

Michael Zitzmann

Abstract

Over the last two decades our insight into testosterone (patho-)physiology has progressed. It is clear that there is an age-related decline of plasma testosterone levels, particularly of non-bound testosterone. In addition, it has become apparent that testosterone (and its metabolic products) have a large number of functions not related to the classical reproductive and sexual actions of testosterone. Hypogonadism can cause osteoporosis, anemia, decrease of lean body mass, increase of body fat content, and a dry skin. There are also a number of psychological complaints such as fatigue, aggressiveness, decrease of cognitive abilities and depression.

Professional organizations have formulated guidelines / recommendations for the administration of testosterone to elderly men. This demonstrates that there is a common agreement among experts in regard for the need to define androgen deficiency in various stages of male life.

Testosterone exerts its actions via testosterone receptors leading to gene transcription. The higher the number of CAG repeats, the lower the transcriptional activity of the androgen receptor. This mechanism impacts on both effects and side effects of testosterone.

Side effects concern mainly the prostate and erythropoeisis, but the currently available literature indicates that there is no increased risk of developing prostate cancer in men receiving testosterone treatment. Following the guidelines as specified by a number of professional organizations, truly testosterone-deficient elderly men can be responsibly treated with testosterone.

Testosterone and its metabolic products, dihydrotestosterone and estradiol, exert a multitude of functions. The common association is that testosterone deficiency impairs only sexual and reproductive functions (decrease of libido, erectile dysfunction, decreased prostate size, decreased spermatogenesis, decreased beard growth and gynecomastia) but over the last decades it has become apparent that testosterone (and its metabolic products) have a large number of further functions [1]. Hypogonadism can cause a multitude of somatic complaints: osteoporosis, anemia, decrease of lean body mass, increase of body fat content, dry skin. There are also a number of psychic complaints such as fatigue, aggressiveness, decrease of cognitive abilities and depression [2,3].

Late onset hypogonadism

Hypogonadism may be primary (testicular failure) or secondary to a deficient production of gonadotrophins by the pituitary gland or of its stimulatory hormone luteinizing hormone-releasing hormone (LHRH) by the hypothalamus, or an in-between form of disturbed feedback. An example of the latter is late-onset hypogonadism (LOH) or mixed hypogonadism. Testosterone (T) deficiency under the age of 50 years is usually due to testicular or hypothalamic-pituitary disease. In men testosterone production is affected in a slowly progressive way as part of the normal aging process. The age-related decline of T will rarely be manifest in men under the age of 50 years and becomes

Michael Zitzmann, MD, PhD
Institute of Reproductive Medicine, University Clinics, D-48149 Muenster, Germany

E-mail:
Michael.Zitzmann@ukmuenster.de

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usually only quantitatively significant in men over 60 years of age [1].

It is still controversial whether the age–related decline of plasma T levels constitutes a true clinical entity and whether this condition needs to be treated with T [4].

There is now growing consensus on the terminology of the age-related decline of testosterone. Male menopause was promptly dismissed by most scientists. Andropause might be a more acceptable term to describe the process of age-related changes in men, but as a term it is not very clear what it stands for. Partial androgen deficiency of the aging male long time dominated terminology but is now replaced by late onset hypogonadism. Very recently the term 'testosterone deficiency syndrome' has been proposed [5], in the case of 'aging' men to be replaced by 'in the elderly'.

Guidelines

Professional organizations have formulated guidelines /recommendations for the administration of testosterone to elderly men. The following overview outlines differences and overlaps between two important sets of guidelines: one adopted by ISA, ISSAM and EAU [6] and one proposed by a task force of the Endocrine Society [7].

This demonstrates that there is a common agreement among experts in regard for the need to define androgen deficiency in various stages of male life. It also shows that the ''clinical feeling'' concerning testosterone deficiency is basically the same all over the world, but that it remains difficult to determine priorities concerning diagnosis and treatment.

Item	ISA, ISSAM and EAU	The Endocrine Society
Methodology	• Based on ISA-sponsored panel discussion at ISSAM congress • No evidence provided for each recommendation No scoring	• Developed by a 6-member Task Force • Evidence-based approach used by the Grading of Recommendations, Assessment, Development, and Evaluation group • Strength of recommendation scored as 'strong' or 'weak' • Quality of evidence scored on 4-point scale from 'very low' to 'high'
Nomenclature	Late-onset Hypogonadism (LOH)	Androgen deficiency syndromes/ hypogonadism
Definition	Clinical and biochemical syndrome characterised by typical symptoms and low testosterone	A clinical syndrome resulting from low testosterone due to disruption of the HPG axis
Symptoms	• Diminished libido and erectile function Depressed mood, fatigue, and reduced cognition Sleep disturbance • Decreased LBM and increased visceral fat • Decrease in body hair and skin changes Decreased BMD resulting in osteopenia, osteoporosis and increased risk of fractures	Reduced libido and erectile function Fatigue Breast discomfort Small or shrinking testes Decreased muscle bulk and strength Decrease in body hair Decreased BMD and increased risk of fractures Hot flushes
Diagnostic Procedures: Biochemical investigation	• Serum total T and SHBG 08:00-11:00 Calculate free T or free T by equilibrium dialysis	Serum total T morning If suspect altered SHBG, calculate free T by measuring SHBG or measure free T by equilibrium dialysis Measure LH and FSH

(*Continued*)

Item	ISA, ISSAM and EAU	The Endocrine Society
Diagnostic Procedures: Assess other disorders	Diabetes ruled out or treated ED – assess lipids and cardiovascular status	Exclude reversible illness, drugs and nutritional deficiency
Therapy nomenclature	Testosterone substitution	Testosterone therapy
Initiate T therapy	Clinical picture plus low T	Older men with clinically significant symptoms and consistently low T after explicit risk-benefit discussion
Aims of therapy	Improvements in signs and symptoms	Improve sexual function, sense of well-being and bone density
Testosterone threshold	Normal Total T >12 nmol/l (346 ng/dl) Free T >250 pmol/l (72 pg/ml) Consider treatment (if symptoms) Total T 8–12 nmol/l (231–346 ng/dl) Low T (requires treatment) Total T <8 nmol/l (231 ng/dl) Free T <180 pmol/l (52 pg/ml)	Low T [no consensus] Total T <6.9–10.4 nmol/l (200–300 ng/dl) Free T <0.17 nmol/l (50 pg/ml)
Contraindications for T	• Suspected or existing carcinoma of the prostate or breast • Polycythaemia, untreated sleep apnoea, severe HF, high IPSS, severe bladder outflow obstruction	• Prostate or breast cancer, or palpable prostate nodule or PSA > 3 ng/ml without further urological evaluation Erythrocytosis, hyperviscosity, untreated sleep apnoea, severe BPH symptoms, uncontrolled severe HF
T preparations	• Any natural T on an individualised basis • Short-acting (transdermal, oral, buccal) preferred over long-acting (IM, subdermal) preparations • Alkylated androgens are obsolete	• Any preparation on an individualised basis • Intramuscular, non-scrotal patch, gel and buccal formulations all recommended

Side effects of testosterone administration

Polycythemia

There is curvilinear relationship in men (not receiving testosterone administration) between plasma testosterone levels and hemoglobin.

Testosterone exerts its effect on erythropoiesis through a number of mechanisms. Testosterone has an effect on erythropoietin production in the kidney [8] but it has also a direct effect on colony formation of progenitor cells of erythrocytes [9]. In a study of Wang [10] a dose dependent effect of testosterone could be established on hemoglobin and the hematocrit. This dose-dependency was also apparent from a study of [11].

Comparing the effects of transdermal versus intramuscular testosterone; the latter achieved higher plasma levels of testosterone and raised the hematocrit more than transdermal testosterone.

The relevance of the increase in hematocrit is the association of an elevated hematocrit with stroke [12], also found in another study [13]. Also an association with coronary heart disease has been found [14]. However, a relation between increased hematocrit as a result of androgen supplementation as such and an increased risk for stroke or any cardiovascular event in general has not been demonstrated by a large meta-analysis of placebo-controlled trials [15].

Prostate disease

The prostate is an exquisitely androgen dependent organ, with a high concentration of testosterone receptors and a high 5-alpha

reductase activity, thus amplifying the action of testosterone on this target organ. Testosterone administration to hypogonadal leads to a (modest) increase in prostate size [16].

Overall, studies, some placebo-controlled, using various testosterone formulations, over periods ranging from several months to 15 years, in men with a wide range of ages, have not revealed an increased risk of prostate cancer [17–27]. A recent meta-analysis found that testosterone treatment in older men compared to placebo was not associated with a significantly higher risk of detection of prostate cancer [15], although the frequency of prostate biopsies was much higher in the *verum*-treated group [15].

The genetics of the androgen receptor

Testosterone exerts its actions via testosterone receptors leading to gene transcription though some effects are non-genomic membrane effects. Complete or partial dysfunctions of the androgen receptor are associated with clinical syndromes, such as the androgen insensitivity syndrome or the Reifenstein syndrome. The gene for the androgen receptor is located on the X-chromosome. In exon 1 there is a variable number of CAG triplet repeats. The higher the number of CAG repeats, the lower the transcriptional activity of the androgen receptor [28,29]. In an experimental model with a human androgen receptor with respectively 12, 21 or 48 CAG repeats, the number of CAG repeats was inversely correlated with the weight of the seminal vesicles, an index of androgen action. By contrast the rate of prostate cancer was lower with the higher numbers of CAG repeats [30].

The issue of CAG repeats and its clinical implications has been reviewed by Zitzmann et al. [31] and indeed the literature provides evidence that androgen effects are modified by the number of CAG repeats of the androgen receptor. Men with lower numbers of CAG repeats are more predisposed to develop prostate cancer [32].

It has to be stressed that both testosterone concentrations and androgen receptor gene CAG repeats exert a non-linear, interactive effect on androgen action (review [33]).

In the presence of normal plasma testosterone levels the effects of testosterone (hairiness, prostate volume) are more pronounced with lower numbers of CAG repeats [34]. While prostate volumes in the hypogonadal state are not strongly affected by the number of CAG repeats, the increase in prostate volume upon testosterone administration to hypogonadal men is inversely correlated with the number of CAG repeats [16]. Similar observations were made during androgen administration to men with Klinefelter syndrome [35].

In summary

Testosterone deficiency is a common but not mandatory condition in elderly men. There are numerous indications that a supplementation therapy has beneficial effects. Special care must be taken concerning the prostate and erythropoeisis, although the currently available literature indicates that there is no increased risk of developing prostate cancer in men receiving testosterone treatment. Following the guidelines as specified by a number of professional organizations, truly testosterone-deficient elderly men can be responsibly treated with testosterone.

Conflict of interest

Dr. Zitzmann declares there is no conflict of interest, and has no funding source to report.

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