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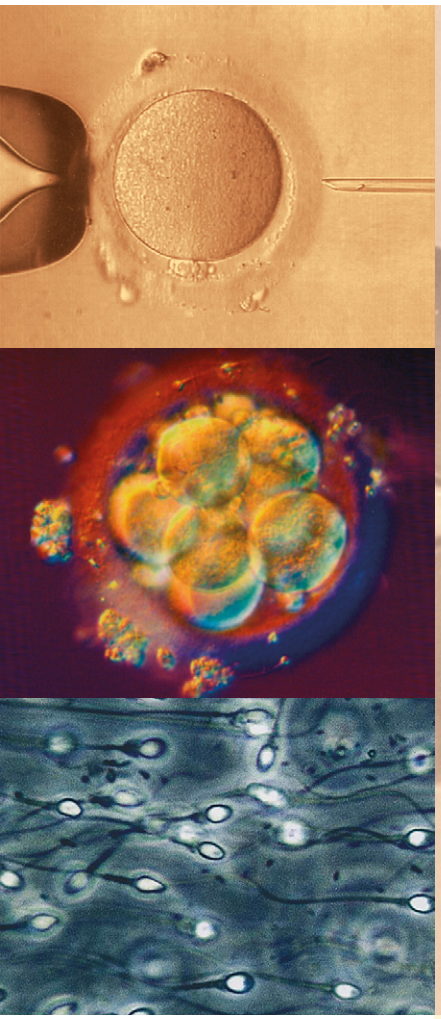

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Testosterone Substitution: Current Modalities and Perspectives

M. Zitzmann, E. Nieschlag

The clinical picture of male hypogonadism is associated with typical symptoms, such as disturbances of mood and cognitive abilities as well as sexual functions; furtheron, a decrease in muscle mass and strength, an accumulation of body fat and osteopenia/osteoporosis are observed. There are indications that insulin sensitivity is mitigated in a state of androgen depletion. In older men, symptoms of androgen deficiency (late-onset hypogonadism) may exhibit a differential profile due to accompanying other chronic illnesses. Restoring serum testosterone levels by replacement therapy can markedly attenuate, if not relieve, the clinical picture of hypogonadism. Recently, new treatment modalities have been introduced, which include short-acting transdermal or buccal modalities as well as the long-acting depot preparation of testosterone undecanoate. This review summarises the pathways of diagnosis of male hypogonadism and discusses the various modern methods of initiation and surveillance of testosterone substitution therapy. Future perspectives regarding pharmacogenetic aspects are discussed. ***J Reproduktionsmed Endokrinol 2006; 3 (2): 109–16.***

Key words: *androgen deficiency, male hypogonadism, testosterone substitution, androgen receptor*

The clinical use of testosterone is substitution therapy of male hypogonadism. This pathological entity manifests itself with a variety of symptoms which are due to a lack of testosterone or its action. Testosterone preparations have been in clinical use for about sixty years. However, only within recent years the clinician has become able to choose from a variety of preparations, which exhibit distinct profiles of short or long acting properties as well as different with pathways of delivery [1, 2].

Replenishment of testosterone resources by such preparations is able to effectively establish, restore, and maintain androgen-dependent functions in males. The start of therapy requires diagnostic procedures to identify the underlying cause of hypogonadism. These procedures must follow standardised and strict pathways, taking both symptoms and various hormone concentrations into account (Fig. 1) [3, 4].

Testosterone substitution therapy has to be accompanied by standardised procedures of surveillance; this refers especially to older men, who may require more frequent clinical controls than younger men [1, 4, 5].

This review summarises the current state of testosterone treatment and gives a concise overview on symptoms and diagnostic procedures related to hypogonadism. Future perspectives relating to pharmacogenetics of testosterone and possible further aspects of androgen actions are considered.

Who Should Be Treated? Modern Approaches to Suspected Hypogonadism

Hypogonadism manifests itself with a variety of symptoms, which can be of psychological, cognitive, sexual, and/or somatic nature. The time of onset may play a role in manifestation patterns of hypogonadism (Tab. 1). Older hypogonadal men usually exhibit characteristics similar to younger patients, but possibly to a lower degree. The pattern of complaints in older men may be caused at least partly by various other chronic illnesses related to the aging process (Tab. 1) [4, 5].

Once a patient presents with symptoms causing suspicion of testosterone deficiency, standardised pathways

Table 1. Symptoms of male hypogonadism (also refer to [1, 4])

Organ/affected function	Onset of hypogonadism before completion of puberty	Onset of hypogonadism after completion of puberty
Larynx	No voice mutation	No change
Hair	Horizontal pubic hair line; straight frontal hair line; diminished beard growth	Diminished secondary body hair; decreased beard growth
Skin	Absent sebum production; lack of acne; pallor; fine skin wrinkling	Decreased sebum production; pallor; fine skin wrinkling
Bone	Eunuchoid tall stature; osteoporosis	Osteoporosis
Haematopoiesis	Anaemia	Anaemia
Breast	Sometimes gynaecomastia	Sometimes gynaecomastia
Muscles	Underdeveloped	Atrophia
Penis	Infantile	No change/atrophy
Prostate	Underdeveloped	Atrophy
Testes	Small volume; often maldescensus	Decrease of volume
Spermatogenesis	Not initiated	Arrest
Mood	Reduced	Reduced
Erectile function and libido	Not developed	Loss

Symptoms typically met in late-onset hypogonadism (LOH)

- Diminished sexual desire and arousability (libido)
- Loss of erectile quality and frequency
- Loss of particularly nocturnal erections
- Depression, fatigue, lack of vigor, irritability
- Decreased intellectual activity: cognitive functions, spatial orientation
- Sleep disturbances
- Decrease in lean body mass, diminution of muscle volume, and strength
- Increase in visceral fat
- Decrease in body hair and skin alterations
- Osteopenia, osteoporosis, and increased risk of bone fractures

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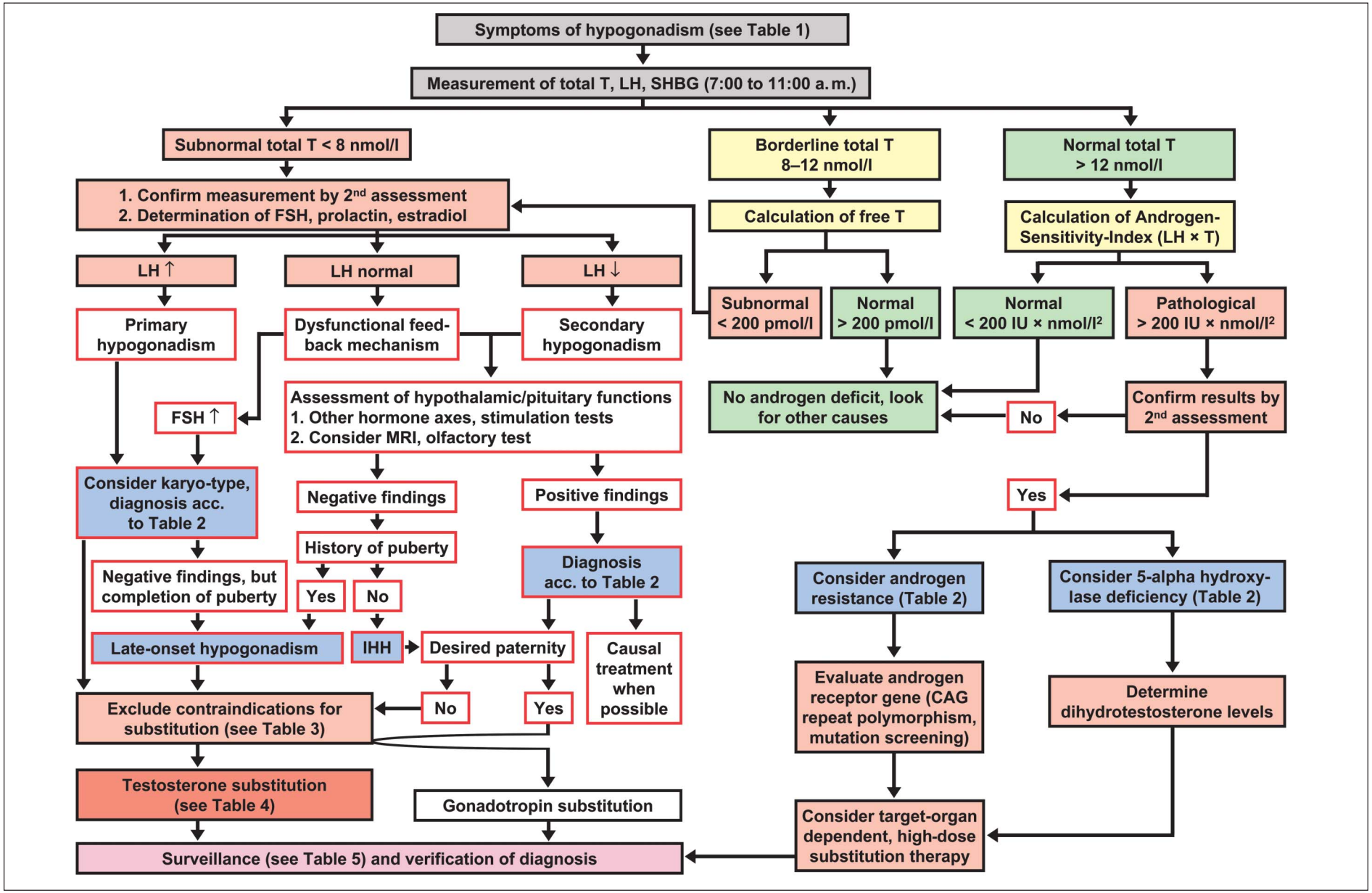

Figure 1. Flowchart of standardised pathways of diagnostics and treatment of male hypogonadism (T = testosterone; SHBG = sex hormone binding globuline; LH = luteinising hormone; FSH = follicle stimulating hormone; MRI = magnetic resonance imaging; IHH = idiopathic hypogonadotropic hypogonadism)

of diagnostics, and therapy should be followed (Fig. 1). Underlying causes of hypogonadism are disorders located at the testicular source of testosterone, the Leydig cells (primary hypogonadism), or at the central regulation unit, consisting of the hypothalamus and the pituitary gland (secondary hypogonadism), the latter secreting luteinising hormone (LH), which stimulates Leydig cells.

Due to the inherent mechanisms of feedback regulation in hormone secretion, primary hypogonadism is usually accompanied by elevated concentrations of LH, while cases of secondary hypogonadism exhibit decreased serum levels of LH. An age-related deterioration as a combined dysfunctionality of both the central and peripheral parts of the androgen regulation system is named "late-onset hypogonadism" (LOH). Depending on the degree, the direction as well as the weighting of pathological processes within such a dysbalance, LOH presents with low to low-normal testosterone concentrations and LH levels which may be slightly decreased, normal or elevated. There is no clear-cut definition of age in relation to LOH; although usually described as disease met in "older" men, the nosology can also be diagnosed in men of "younger age".

Hypogonadal symptoms also occur in cases of target organ resistance, mostly due to inherited alterations of the androgen receptor; in this case, elevated concentrations of both testosterone and LH are found and the androgen-sensitivity index is elevated, pointing to androgen resistance (see below, pharmacogenetic implications) (overview: Tab. 2; pathway of diagnosis: Fig. 1) [1, 6, 7].

For diagnostic purposes in suspected hypogonadism, assessment of total testosterone, luteinising hormone (LH), follicle stimulation hormone (FSH), prolactin, and estradiol is helpful, as well as calculation of free testosterone from total testosterone and sex hormone binding globulin [8], this complete overview of hormones classifies the clinical picture in regard to fertility and estrogen-related features of the phenotype (e. g. fat distribution, gynaecomastia, bone density) (Fig. 1). Determination of androgen receptor genotype and concentrations of serum dihydrotestosterone will be applied in special cases of suspected androgen resistance (Fig. 1).

Questionnaires related to possible androgen deficits are not useful for screening purposes because of their low sensitivity and specificity [5]. Nevertheless, such tools may be useful for monitoring purposes during testosterone substitution therapy.

Modalities of Testosterone Substitution

Once the diagnosis of hypogonadism has been established, testosterone substitution treatment is recommended after consideration of absolute and relative contraindications (Tab. 3). For such therapy, the natural hormone has to be selected to provide all physiological functions of testosterone and its metabolites estradiol and dihydrotestosterone. An exception is the desired simultaneous induction of fertility in secondary hypogonadism; in this case gonadotropins have to be administered, since external androgens cannot induce spermatogenesis (see below). Rather, externally administered testosterone acts as a contraceptive agent as it suppresses the secretion of gonadotropins [9].

Table 2. Overview of main disorders with male hypogonadism

Primary hypogonadism	Secondary hypogonadism	Androgen resistance
• Anorchia • Maldescensus testis • Orchitis • Klinefelter syndrome; 47,XXY • XX-male syndrome • Leydig cell tumors • LH-receptor defects • Chronic disease • Testicular trauma • Testicular radiation • Chemotherapy	• Idiopathic hypogonadotropic hypogonadism (IHH) • Kallmann syndrome • Pituitary adenoma • Chronic disease • Haemochromatosis • Central ischaemia • Cerebral trauma • Radiation of cerebral areas during tumor therapy • Cachexia • Opioid medication or abuse • GnRH-receptor mutations	• Mutations of the androgen receptor • Long androgen receptor gene CAG repeats (> 25 ?) • 5-alpha-reductase insufficiency
Mixed primary and secondary hypogonadism Late-onset hypogonadism (LOH)		

Table 3. Absolute and relative contraindications for testosterone substitution

Absolute contraindications	Relative contraindications
• Prostate carcinoma or suspicion thereof • Breast carcinoma or suspicion thereof • Desired paternity • Criminal sexual behaviour • Unclear polycythosis • Untreated sleep apnea • Severe symptoms of lower urinary tract obstruction • Severe heart failure	• Benign prostate hyperplasia • Mild polycythosis • Acne • Competitive sports • Unclear liver disease • Unclear renal disease • Treated sleep apnea • Mild symptoms of lower urinary tract obstruction • Unclear gynaecomastia

Table 4. Currently available testosterone preparations

Pathway of application	Generic name	Trade name	Dose
Oral	Testosterone undecanoate	Andriol Testocaps	2 capsules 2–3 times/d
Transdermal	Testosterone patch	Androderm	2 × 5 mg/d
	Testosterone gel 25 mg or 50 mg	Testogel	50–100 mg/d
	Testosterone gel 25 mg or 50 mg	Androtop Gel	50–100 mg/d
	Testosterone gel 50 mg	Testim	50–100 mg/d
Intramuscular	Testosterone enanthate 250 mg	Testosterone Depot 250	1 ampoule every 2–3 weeks
	Testosterone undecanoate 1000 mg	Nebido	1 ampoule every 10–14 weeks (see text for loading dose)
Buccal	Testosterone 30 mg	Striant	1 tablet 2 times/d
Implants	Testosterone 200 mg	Testosterone Implant 200 mg	3–5 pellets every 4–6 months

An overview of currently available testosterone preparations including generic as well as trade names and standard dosing is given in Table 4.

Oral Pathway
Testosterone undecanoate is an ester which can be administered orally; the route of absorption is lympathic, it thus reaches circulation via the thoracic duct. Kinetics and absorption pathways require ingestion of the preparation 2–3 times per day simultaneously with a fat-containing meal. This substance has been in use for more than three decades and can be safely administered in cases of mild hypogonadism [2, 10, 11].

Transdermal Pathways
Testosterone patches are able to imitate the circadian secretion rhythm and can raise serum concentrations into the normal range. Evidence is still lacking that mimicking the physiological secretion translates into a clinical benefit. Drawbacks of these patches are their visibility and a significant potential for skin irritation. Due to their inherent kinetics, the patches should be applied daily during evening hours and be worn for at least 20 hours [2, 11, 12].

Testosterone gel preparations are based on hydroalcoholic carriers and can reliably provide serum concentrations within the normal range. Resorption exhibits interindividual variability and dosing should be adapted according to effects and serum levels (Tab. 4). This short-acting method of testosterone substitution is applied daily and is recommended for cases in which rapid responses to treatment effects might be required, such as in older men initiated on therapy, to facilitate proper handling of side effects/contraindications (e. g. prostate disease or polycythaemia) (see below). Interpersonal transfer is unlikely after evaporation of the alcoholic vehicle [2, 4, 11, 13, 14].

Intramuscular Pathways
Testosterone enanthate is a still widely used preparation for testosterone substitution. This substance has a terminal half-life of 4.5 days; maximum concentrations are reached after 10 h following a single intramuscular injection of 250 mg. Multiple-dose pharmacokinetics reveal an optimal injection interval of 2–3 weeks at a dose of 250 mg, but peak and trough values continue above/below the normal range. Having been in use for about 50 years, the substance is reliable, but patients sense fluctuations of androgen concentrations [2, 11].

Testosterone undecanoate: this new form of a long-acting testosterone preparation for intramuscular injection has recently been made available. 1000 mg of testosterone undecanoate dissolved in castor oil are injected intramuscularly about 4 times per year. To achieve a fast steady-state following initiation of therapy, the second injection has to be given after 6 to 10 weeks. Thereafter, the dosing interval can be prolonged, reaching 10 to 14 weeks. This procedure should be based on serum trough levels determined prior to the following injection. In terms of treatment effects, intramuscular testosterone undecanoate proved to be as efficient and reliable as the short-acting ester testosterone enanthate, while simultaneously avoiding unfavourable peak levels and periods of insufficient (i. e. low) testosterone concentrations. Thus, sensing of fluctuations as well as side-effects related to high peak levels (e. g. elevated haematocrit under testosterone enanthate [15]) can be avoided [16]. The substance, as the orally administered preparation, revealed no unexpected side effects and is usually well tolerated. Testosterone undecanoate should be injected slowly into the gluteal muscle [2, 11, 17–20].

Implants
Subdermal implants of testosterone pellets were among the first treatment modalities of hypogonadism [21]. With the advent of modern modalities, e. g. long-acting intramuscular injections, they went out of general use but are still available. The standard dose is implantation of 3 to 5 pellets containing 200 mg testosterone every 4 to 6 months, which should be titrated individually. Side effects are extrusions, bruising, and infections [2, 11, 22, 23].

Buccal Pathway
A mucoadhesive system of testosterone and bioadhesive excipients can be applied to the buccal mucosa and thus evades first-pass clearance in the liver. This new method of testosterone substitution exhibits reliable kinetics when applied twice daily to the upper gums. Serum concentrations of testosterone induced by this application are higher than those achieved by patches and comparable to the gel preparations. In patients requiring short-acting substitution and exhibiting skin irritations caused by transdermal products, this is a favourable alternative [2, 11, 24].

Gonadotropin Substitution
This form of therapy is reserved for fertility induction in cases of secondary hypogonadism. As external testosterone is not able to stimulate spermatogenesis, the gonadotropins LH, and FSH or analogues have to be administered by subcutaneous injections to stimulate both Leydig cells and Sertoli cells. Dosing should be guided by testicular growth, androgenisation, and testosterone levels, as well as inhibin B concentrations and appearance of sperm in the ejaculate. In cases of hypothalamic disorders, pulsatile treatment with GnRH may be considered. Gonadotropin treatment requires a high level of expertise and should be restricted to specialised centres [25, 26]. There are several modalities and preparations to perform such a treatment (comparative overview: [27]).

Benefits of Testosterone Substitution

When hypogonadism is treated by testosterone substitution therapy, symptoms caused by androgen deficiency (Tab. 2) can be expected to vanish or be ameliorated. This may require some time depending on the target organ, but effects on mood and sexuality are usually seen within weeks.

Favourable mood changes in terms of lower rates of "negative feelings", even amelioration of depressive components, as well as sensing more vigour and energy will occur upon testosterone substitution [1, 5, 28, 29]. Moreover, aspects related to sexuality, such as libido, quality of sexual life, and frequency as well as quality of erections improve upon replenishment of testosterone

Table 5. Surveillance of testosterone therapy

Surveillance target	Measure	Interval first year#	Interval following years*	Threshold (action required)
Blood viscosity	Haematocrit	Every 3 months	1 or 2 times per year	52 % (dose reduction)
Prostate	Size (TRUS)	Every 3 months	1 or 2 times per year	Symptoms of obstruction (dose reduction and other therapy)
	Palpation	Every 3 months	1 or 2 times per year	Pathological finding (withdrawal/biopsy)
	PSA	Every 3 months	1 or 2 times per year	4 ng/ml or PSA velocity > 0.4 ng/ml/year after 1st year and absolute PSA > 1 ng/ml (withdrawal/biopsy)
Hair	Observation	Every 6 months	Annually	Undesired balding (dose reduction or change of preparation)
Sleep	Question or sleep monitoring	Every 6 months	Annually	Sleep apnea (dose reduction and adequate therapy)
Skin	Observation	Every 3 months	Annually	Acne/irriation (dose reduction or change of preparation)
Lipids	Total cholesterol, triglycerides, HDL-C, LDL-C	Every 6 months	Annually	In case of no favourable effects, consider increment of dose and determination of CAG repeat androgen receptor polymorphism
Bone	Densitometry	After 1 year	Every 2 years	
Sexuality	Question	Every 3 months	1 or 2 times per year	
Mood	Question	Every 3 months	1 or 2 times per year	

In men younger than 40 years, surveillance may be performed at 3 months and 9 months after start of therapy; * only in case of normal findings, otherwise 1st year-intervals apply after change of dose; TRUS = transrectal ultrasound

resources [29]. Cognitive abilities, especially in regard to processing spatial information, increases during testosterone substitution [30]. Pathways of the so-called ventral processing stream involved in higher evaluation of visual content are activated by androgens [31].

Testosterone treatment can significantly reduce body fat content in hypogonadal men, and vice versa, it can increase lean body mass, a phenomenon not only due to shifts in proportions, but also to absolute growth of muscle tissue. These processes follow a log-linear dose-response relationship to testosterone [29, 32–34]. As bone tissue metabolism is positively affected by testosterone and its aromatisation product estradiol, substitution therapy of hypogonadal men improves bone density. The process is visible after 6 months, but usually takes 2 to 3 years to reach steady-state [29, 35]. It is mostly due to shifts in trabecular architecture [36, 37].

Hypogonadal men often present with anaemia. Irrespective of the preparation used, elevation of testosterone levels will increase haemoglobin levels in these patients [29, 38]. Substitution effects when using intramuscular testosterone undecanoate will reach a plateau after approximately 6 to 9 months [19]. A marked variability of the haematopoietic system to respond to testosterone exists, which underlines the necessity for surveillance: in some, and in particular older, men unacceptably high levels of haemoglobin and haematocrit can develop, so that the dosage has to be adjusted to prevent adverse vascular events. Such side-effects are usually seen during application of short-acting intramuscular preparations, i. e. testosterone enanthate [15].

Surveillance of Testosterone-substituted Men

Table 5 gives an overview concerning time points and surveillance parameters during testosterone substitution therapy. Surveillance of older men should consider the ISSAM/ISA/EAU recommendations on LOH [4].

The prostate is an androgen-dependent organ and will generally increase in size during testosterone substitution therapy. An elevation of PSA concentrations is usually seen upon initiation of treatment. As prostate cancer and benign prostate hyperplasia have a high incidence in men, careful screening by measurement of PSA, accompanied by digital rectal exams and, if possible, transrectal ultrasound (TRUS) are recommended within fixed intervals (Tab. 5).

Pathological findings and/or PSA levels > 4 ng/ml should lead to (temporary) testosterone withdrawal and to the consultance of a specialised urologist as well as possible prostate biopsy [1, 4]. In addition, changes of PSA levels over time, i. e. PSA velocity, are a useful tool to assess testosterone effects on the prostate: also in cases of PSA levels < 4 ng/ml, (temporary) testosterone withdrawal and urological consultance/prostate biopsy are advisable if following prerequisites are met:

a) testosterone substitution has been performed for more than 1 year,
b) absolute PSA is > 1 ng/ml,
c) PSA velocity is > 0.4 ng/ml/year (according to [39]).

Haematocrit will increase during testosterone substitution of hypogonadal men (see above). It should not ex-

ceed 50–52 % as the risk for ischaemic events is increased beyond that threshold [40] and should be checked regularly (Tab. 5). Testosterone preparations avoiding high peak levels are usually safer in this regard [15].

Testosterone affects lipid metabolism and substitution therapy is capable of inducing shifts in lipoprotein subfractions [41]. These changes can be of mixed nature and the relation to cardiovascular risk remains unclear [42]. Lipid profiles should be assessed according to Table 5 and possibly regulated by additional medications (e. g. statins). Factors exerting adverse effects on the cardiovascular system (cigarette smoking, arterial hypertension, inflammation) should be eliminated anyway.

Future Perspectives

Metabolic Syndrome/Diabetes Mellitus Type 2/Cardiovascular Risk/Inflammation

These catchwords relate to each other within a nosological complex increasingly observed in affluent countries and are connected to obesity and a sedentary life-style. Type 2 diabetes mellitus is an increasing pathological entity and represents an established risk factor for the development of atherosclerotic vascular disease. Insulin resistance is the hallmark feature of type 2 diabetes and is simultaneously an important component of the metabolic syndrome, a pre-clinical condition also including high visceral fat content, arterial hypertension and an inflammatory status. There is evidence to suggest that testosterone is an important regulator of insulin sensitivity in men. Observational studies have shown that testosterone levels are low in men with diabetes, visceral obesity, coronary artery disease and the metabolic syndrome. Short-term interventional studies support the assumption that testosterone replacement therapy in hypogonadal men induces respective clinical improvements, also concerning inflammatory markers and cardiac status. Hypogonadism may play a role in the pathogenesis of insulin-resistant states and androgen replacement therapy could be a potential treatment for improvements in glycaemic control and reduction of cardiovascular risk, particularly in diabetic men [43–49]. Nevertheless, long-term studies are required to determine the potentially beneficial role of testosterone in this regard.

Erectile Dysfunction

Arterial integrity is a key component for penile cavernous vasodilation, a process leading to erection and directly regulated by androgens. It has been demonstrated that erectile dysfunction is an early marker of cardiovascular events [50, 51]. Especially in hypogonadal patients, the therapeutic approach with phosphodiesterase type 5 (PDE-5) inhibitors often proves unsuccessful. There is some evidence that additional testosterone treatment in men with erectile dysfunction and low androgen levels is synergistic to PDE-5 inhibitors, especially in diabetic patients [52–54].

Pharmacogenetic Implications

Cases of androgen resistance (Fig. 1) are often characterised by an elevated androgen-sensitivity index and by features of hypogonadism. Such patients often exhibit genetic alterations of the androgen receptor, leading to a dysfunctional receptor protein and reduced/aborted testosterone action. The clinical picture may be overcome by high-dose testosterone treatment, titrated to effects in androgen target-organs [6, 7, 55, 56].

Subtle modulations of the transcriptional activity induced by the androgen receptor have also been observed and frequently assigned to a polyglutamine stretch of variable length within the N-terminal domain of the receptor protein. This stretch is encoded by a variable number of CAG-triplets in exon 1 of the AR gene, which is located on the X-chromosome. Longer triplet residues mitigate binding of the androgen receptor to co-activators and facilitate decreased androgenicity. An influence of the polymorphism on androgen target tissues such as the prostate, spermatogenesis, bone, hair, metabolic parameters, and psychological factors has been demonstrated [57–62]. Men presenting with features of hypogonadism may exhibit normal testosterone levels but CAG repeat lengths above the normal average (Europe: 21; Africa: 17; Asia: 23). A CAG repeat length longer than 25 is still considered to be within the normal range, but is most likely associated with reduced androgen action and accompanying clinical features [63].

Extending these findings to pharmacogenetic considerations, a possible modulation of androgen effects during testosterone administration has to be considered. This aspect could gain clinical significance, especially in older men, as these patients are more likely to develop unwanted androgen-related side-effects. In regard to prostate enlargement in over 130 hypogonadal men initiated on testosterone substitution therapy, we demonstrated that prostate growth and volume were markedly influenced by the CAG repeat polymorphism. The findings were more pronounced in men older than 40 years and seem to put patients with a repeat chain of 20 or less triplets at an increased risk of developing an enlarged organ [64]. Treatment of alopecia is also affected by this polymorphism [65].

In Klinefelter patients who have two androgen receptor alleles, the shorter CAG repeat allele is preferentially inactive. In this group of patients with primary hypogonadism: CAG repeat length is positively associated with body height. Bone density and the relation of arm span to body height are inversely related to CAG repeat length. The presence of long CAG repeats is predictive for gynaecomastia and smaller testes, while short CAG repeats are associated with a stable partnership and professions requiring higher standards of education (also when corrected for family background). There is a trend for Klinefelter men with longer CAG repeats to be diagnosed earlier in life. Under testosterone substitution, these men with shorter CAG repeats exhibit a more profound suppression of LH levels, augmented prostate growth and higher haemoglobin concentrations [66]. Intra-uterine androgen effects seem to be modulated by this polymorphism, as demonstrated by alterations of the phenotype of Klinefelter boys [67]. These pharmacokinetic findings may provide the basis for individualised testosterone substitution therapy by adjusting the dose to the androgen receptor polymorphism and effects in target-organs.

Conclusion

Hypogonadism in men represents a disease which leads to a marked decrease in quality of life and exposes the

patients to further health risks. Physicians have been provided with a wide range of treatment options. Diagnosis should follow standardised pathways, as well as treatment modalities and surveillance.

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