Chapter

14 Clinical use of testosterone in hypogonadism and other conditions

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14.1 Use of testosterone in male hypogonadism

The primary clinical use of testosterone is substitution therapy for male hypogonadism. Hypogonadism may be caused by lesions of the hypothalamo-pituitary system (secondary hypogonadism), the testes themselves (primary hypogonadism) or a mixture of both as in LOH. Lesions in the target organs may also cause hypogonadism (see Chapters 3 and 19). An overview of the various disease entities and syndromes is provided in Table 14.1, and for a detailed description the reader is referred to the textbook in andrology by Nieschlag *et al.* (2010). In recent years it became clear that there are strong interrelationships between hypogonadism on the one side and the metabolic syndrome as well as cardiovascular disorders on the other side; two special chapters (10 and 11) are therefore dedicated to these exciting developments.

The clinical signs and symptoms of all syndromes and disease entities are predominantly due to a lack of testosterone or its action. The most frequent disorders requiring testosterone substitution are Klinefelter syndrome (incidence 1 in 500 men), Kallmann syndrome, isolated hypogonadotropic hypogonadism (IHH), late-onset hypogonadism (LOH), anorchia and pituitary insufficiency. Some disorders such as varicocele, orchitis, maldescended testes and Sertoli-cell-only syndrome may not, or only eventually, require testosterone substitution. Although discrete endocrine alterations may be noted by laboratory tests in these patients, the endocrine capacity of the Leydig cells remains high enough to maintain serum testosterone in the lower physiological range.

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Table 14.1 Overview of disorders with male hypogonadism classified according to localization of cause

Hypothalamic-pituitary origin (hypogonadotropic syndromes = secondary hypogonadism)
Isolated hypogonadotropic hypogonadism (IHH) including Kallmann syndrome
Congenital adrenal hypoplasia
Prader–Labhart–Willi syndrome
Laurence–Moon–Biedl syndrome
Constitutional delay of puberty
Pituitary insufficiency/adenomas
Pasqualini syndrome
Isolated lack of FSH
Biological inactive LH or FSH
Hyperprolactinemia
Hemochromatosis
Testicular origin (hypergonadotropic syndromes = primary hypogonadism)
Congenital anorchia
Acquired anorchia
Maldescended testes
Klinefelter syndrome
XYY syndrome
XX male
Gonadal dysgenesis
Testicular tumors including Leydig cell tumors
Varicocele
Sertoli-cell-only syndrome
General disease e.g. renal failure, liver cirrhosis, metabolic syndrome, diabetes, myotonia dystrophica
Disorders of sexual differentiation due to enzyme defects in testosterone biosynthesis or LH-receptor defects (Leydig cell aplasia)
Exogenous factors
Mixed primary and secondary hypogonadism
Late-onset hypogonadism
Target organ resistance to sex steroids
Complete androgen insensitivity (CAIS) (testicular feminization)
Reifenstein syndrome (partial androgen insensitivity; PAIS)
Perineoscrotal hypospadias with pseudovagina
Aromatase deficiency
Estrogen resistance
Gynecomastia

In order to achieve fertility in patients with hypothalamic (IHH) or pituitary insufficiency, treatment with gonadotropins (hCG/hMG) or pulsatile GnRH is required temporarily (e.g. Büchter *et al.* 1998; Depenbusch *et al.* 2002; Warne *et al.* 2009). Once a pregnancy has been induced these patients will go back on testosterone substitution. Individuals with hypogonadism of testicular origin in whom infertility cannot be treated require testosterone substitution continuously. In all these patients testosterone substitution is a lifelong therapy.

There is general agreement that patients with "classical" disorders of primary or secondary hypogonadism should receive testosterone substitution therapy. However, there is a relatively large group of patients in whom hypogonadism develops as a corollary of other acute or chronic diseases. Although these patients lack testosterone and show symptoms of hypogonadism, testosterone is usually not administered to them. Just why substitution is withheld is not quite clear. Probably in many physicians' minds testosterone is still predominantly associated with sexual functions. However, the better the general effects of testosterone on well-being, mood, bones, muscles and red blood are understood, the more frequently testosterone substitution will be considered. Chapter 17 is dedicated to the possible use of testosterone in these non-gonadal diseases. Similarly, LOH occurring with increasing incidence in aging men, and representing a combined form of primary and secondary hypogonadism, is associated with symptoms of testosterone deficiency. But there is no general agreement on treatment strategies of this condition, and Chapter 16 deals with LOH and the controversies and unresolved problems surrounding this area. Chapter 18 analyses and compares the various guidelines for treatment of testosterone deficiency issued by different societies and organizations. As is stated there, most of the recommendations are not strictly evidence based, and clinical experience prevails as the major criterion. Therefore, for the time being, the principle may be followed that any type of hypogonadism documented by decreased serum testosterone concentrations deserves testosterone substitution, unless there is a clear contraindication, of which there are only a few.

14.1.1 Classification and symptoms of hypogonadism

The time of onset of testosterone deficiency is of greater importance for the clinical symptoms than localization of the cause. Lack of testosterone or testosterone action during weeks 8 to 14 of fetal life, the period of sexual differentiation, leads to the development of intersexual genitalia (see Chapter 3). Lack of testosterone at the end of fetal life results in maldescended testes and small penis size. In later life the onset of testosterone deficiency before or after completion of puberty determines clinical appearance (Table 14.2).

If testosterone is lacking from the time of normal onset of puberty onwards, eunuchoidal body proportions will develop; i.e. arm span exceeds the standing height, and lower length of body (from soles to symphysis) exceeds upper length (from symphysis to top of the cranium), and bone mass will not develop to its normal level. The distribution of fat will remain prepubertal and feminine; i.e. emphasis of hips, buttocks and lower belly. Voice mutation will not occur. The frontal hairline will remain straight without lateral recession; beard growth is absent or scanty; the pubic hairline remains straight. Hemoglobin and erythrocytes will be in the lower-normal to subnormal range. Early development of fine perioral and periorbital wrinkles is characteristic. Muscles remain underdeveloped. The skin is dry due to lack of sebum production, and free of acne. The penis remains small; the prostate is underdeveloped. Spermatogenesis will not be initiated, and the testes remain small. If an ejaculate can be produced it will have a very small volume. Libido and normal erectile function will not develop.

A lack of testosterone occurring in adulthood cannot change body proportions, but will result in decreased bone mass and osteoporosis, as well as in accumulation of abdominal fat. Early-on, lower backache and, at an advanced stage, vertebral fractures may occur.

Once mutation has taken place the voice will not change again. Lateral hair recession and baldness when present will persist, the secondary sexual hair will become scanty and, in advanced cases, a female hair pattern may again develop. Mild anemia may develop. Muscle mass and power decrease. The skin will become atrophied and wrinkled. Gynecomastia may develop. The prostate will decrease in volume while the penis will not, or only minimally, change its size, but will lose its function for coitus (Chapter 12). Spermatogenesis will decrease and, as a consequence, also the size of the testes, which will become softer. Libido and sexual arousability will decrease or disappear, while potency will be less affected.

14.1.2 Initiation of substitution therapy and choice of preparation

Testosterone substitution is started when the diagnosis is established and serum testosterone levels below

Table 14.2 Symptoms of hypogonadism relative to age of manifestation

Affected organ/function	Onset of lack of testosterone	
	Before	**After**
	completed puberty	
Larynx	No voice mutation	No change
Hair	Horizontal pubic hairline, straight frontal hairline, diminished beard growth	Diminishing secondary body hair, decreased beard growth
Skin	Absent sebum production, lack of acne, pallor, skin wrinkling	Decreased sebum production, lack of acne, pallor, skin wrinkling, hot flashes
Bones	Eunuchoid tall stature, arm span > height, osteoporosis	Arm span = height, osteoporosis
Bone marrow	Low degree anemia	Low degree anemia
Muscles	Underdeveloped	Atrophy
Prostate	Underdeveloped	Atrophy
Penis	Infantile	No change of size, loss of function
Testes	Small volume, often maldescended testes	Decrease of volume and consistency
Spermatogenesis	Not initiated	Arrest
Ejaculate	Not produced	Low volume
Libido	Not developed	Loss
Erectile function	Not developed	Erectile dysfunction

the normal range are found, taking into account the various influences on serum testosterone levels, including diurnal variations. In order to establish a diagnosis by documenting low serum testosterone levels, usually determination of testosterone in a serum sample taken between 07.00 and 11.00 in the morning is sufficient (Vermeulen and Verdonck 1992). Pooled sera will not improve diagnostic accuracy (see Chapter 4).

The symptoms of androgen deficiency can be prevented or reversed by testosterone treatment. It is important that a preparation with natural testosterone is selected for treatment so that all functions of testosterone and its active metabolites, DHT and estradiol, can be exerted (Fig. 14.1). Of all testosterone preparations and routes of application described in Chapter 15, im injection or oral ingestion of testosterone esters were formerly the most widely accepted and practiced modalities for the treatment of all forms of hypogonadism. Over the last two decades, transdermal testosterone preparations have become a valuable alternative, first transdermal patches and, more recently, transdermal gels. The transdermal preparations have the advantage that at least some mimic the normal physiological diurnal rhythm and thus represent the most physiological form of substitution.

For full im substitution, pharmacokinetic and clinical studies show that 200–250 mg testosterone enanthate or testosterone cypionate must be injected every two weeks (Nieschlag *et al.* 1976; Schulte-Beerbühl and Nieschlag 1980; Snyder and Lawrence 1980; Sokol *et al.* 1982; Cunningham *et al.* 1990). More recently, testosterone undecanoate dissolved in castor oil and injected intramuscularly has been shown to be effective in substitution therapy (Behre *et al.* 1999a; von Eckardstein and Nieschlag 2002; Zitzmann and Nieschlag 2007; Brabrand *et al.* 2011). Peak values remain within the normal range. In order to achieve a steady state at the beginning of substitution, the second 1000 mg injection is given 6 weeks after the first; further injections follow 10–14 weeks later. Individual intervals are determined according to serum testosterone levels which are measured immediately before the next injection. These determinations are then repeated in yearly intervals. Values

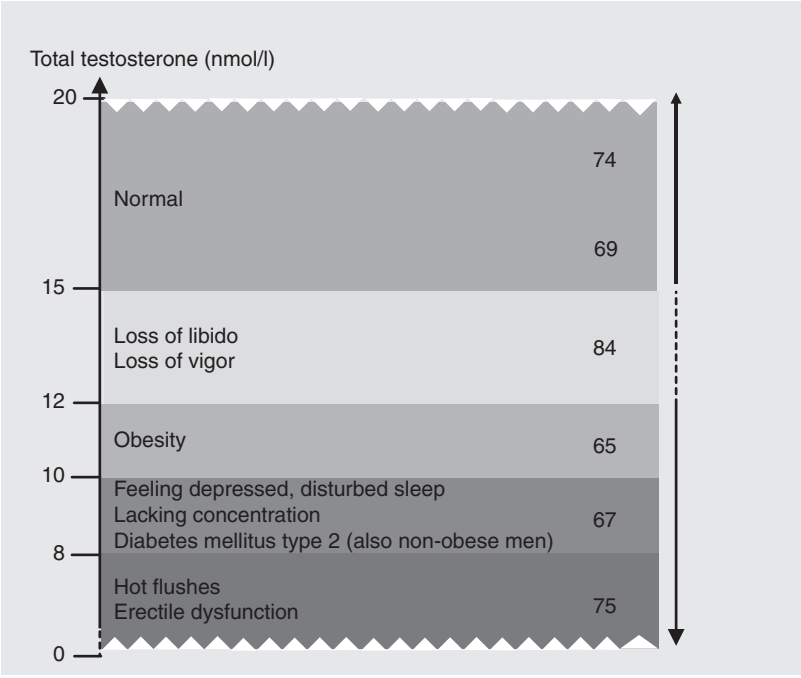

Fig. 14.1 Threshold levels of serum testosterone for various symptoms of late-onset hypogonadism (LOH) in 434 patients (Zitzmann *et al.* 2006). See plate section for color version.

that are too high lead to extension of injection intervals, and those that are too low to a shortening in injection intervals. Slow intergluteal injections are recommended. No adverse side-effects have been observed, even after many years of use (Zitzmann and Nieschlag 2007). If the dose of testosterone undecanoate injected is lowered, e.g. to 750 mg, the injection intervals need to be shortened to maintain normal serum levels (Wang *et al.* 2010).

Testosterone pellet implants were among the first modalities applied for TRT (see Chapter 1). If three to six implants are inserted, slowly declining serum testosterone levels in the normal range are achieved for four to six months. There is, however, an initial burst release, so that supraphysiological levels of about 50 nmol/l result. Commercially, pellets are only available in a few countries.

If oral substitution is preferred, 40 mg testosterone undecanoate capsules must be given two to four times daily. These doses have been shown to be effective in the majority of hypogonadal men in either open (Franchi *et al.* 1978; Morales *et al.* 1997) or double-blind controlled studies (Luisi and Franchi 1980; Skakkebaek *et al.* 1981) when libido and potency as well as physical and mental activity were taken as parameters. Although relatively high testosterone doses are consumed with this regimen, liver function is not negatively affected, as was shown in 35 men taking 80–200 mg testosterone undecanoate over 10 years (Gooren 1994). The patients need to be instructed to ingest the capsules together with a meal in order to guarantee adequate absorption from the gut (Bagchus *et al.* 2003).

Transdermal testosterone preparations mimic physiological diurnal variations, and their kinetic profile is closest to the ideal substitution. They may be used as first choice and are especially well suited for patients who suffer from fluctuating symptoms caused by other preparations. In addition, upon removal, testosterone is immediately eliminated and they are therefore specifically suited for substitution in advanced age (Wang *et al.* 2008).

Scrotal patches consisting of a thin film containing 15 mg native testosterone were the first on the market. They were applied daily in the evening and led to sufficient serum testosterone levels for 22–24 hours. Adequate long-term substitution effect was achieved without serious side-effects under regular use, as has been observed in patients treated for up to 10 years with these patches (Behre *et al.* 1999b). Later developments superseded this initially useful preparation.

Non-scrotal transdermal systems also result in physiological serum levels with an appropriate

number of systems, which have to be applied in the evening. As resorption of testosterone depends on the use of enhancers, in some cases considerable skin reactions limit the use of the systems. Although the patches mentioned above are hardly used today, recently a new testosterone patch was developed causing little skin irritation and which must be changed only every other day; however, two systems with either 1.8 or 2.4 mg resorbed per day must be used (Raynaud *et al.* 2009).

A further transdermal application is the use of testosterone gels, which are applied to large skin areas in order to allow sufficient amounts of the hormone to be resorbed. These gels are applied in the morning to the upper arm, shoulders and abdomen and are left to dry for five minutes. During this time contact with women or children, direct as well as through washrags and towels (de Ronde 2009), must be avoided, because of the danger of contamination. Thereafter the danger is negligible especially if the skin is washed after evaporation of the alcohol. Physiological levels result when the gel is applied in the morning. Long-term use over several years showed good results (Wang *et al.* 2004; McNicholas and Ong 2006). If a preparation with a higher testosterone concentration is used, less gel needs to be applied and good clinical results are obtained. If this gel is applied to the scrotum, only one fifth of the amount required when used on other skin areas is necessary for substitution (Kühnert *et al.* 2005). However, the scrotal application has not yet been licensed.

The choice of testosterone preparation and route of administration is ultimately up to the patient, who over time may gather experience with several preparations and develop his own preference. Younger patients will be more inclined to choose long-acting preparations, while the older patient (> 50 years) should be advised to use a short-acting preparation at least initially (Wang *et al.* 2008). If therapy has to be stopped due to developing contraindications (e.g. prostate disease), serum testosterone levels will immediately decline to endogenous levels.

If a patient has pronounced androgen deficiency, has never received testosterone and has passed the age of puberty, he is immediately treated with a full maintenance dose of testosterone. In cases of secondary hypogonadism when fertility is requested, testosterone therapy can be interrupted and GnRH or hCG/hMG therapy can be implemented until sperm counts increase and a pregnancy has been induced. Testosterone therapy does not prevent the chance of initiating or reinitiating spermatogenesis with releasing or gonadotropic hormones. Once spermatogenesis has been induced it can be maintained for some time with hCG alone, keeping intratesticular testosterone concentrations high (Depenbusch *et al.* 2002).

Patients with residual testosterone production may not require a full maintenance dose, e.g. Klinefelter patients in an early phase of testosterone deficiency. In these cases injection intervals of testosterone esters may be extended; these cases may also be suited for low-dose testosterone undecanoate therapy (i.e. 40 mg once or twice daily) or intermittent transdermal treatment (e.g. every second or third day). This dose does not entirely suppress the residual endogenous testosterone production and supplements the lacking hormone.

Finally, the question needs to be addressed at which serum testosterone levels substitution therapy should be initiated. Based on clinical experience and many studies in normal and hypogonadal men, we considered 12–40 nmol/l as the normal range for many years (Nieschlag *et al.* 2010), i.e. starting treatment when – in the presence of relevant symptoms – testosterone levels dropped below 12 nmol/l. However, in other countries different levels were considered to be the limit to start substitution; e.g. 7.5 nmol/l in France, 7.5 to 8.0 nmol/l in the UK and 9.0 nmol/l in Spain (Nieschlag *et al.* 2004). This prompted a systematic investigation in patients suspected of LOH, and symptom-specific testosterone threshold levels resulted (Fig. 14.1). With regard to the different lower limits of normal, this implies that physicians consider different symptoms as an indication to start substitution, and the lower limit of 12 nmol/l could be raised rather than lowered. The 12 nmol/l threshold received further support from a recent study on reference ranges for normal men based on several cohorts and liquid chromatography–tandem mass spectrometry leading to 12.1 nmol/l (= 348 ng/dl) as the lower limit of normal (2.5th percentile (Bhasin *et al.* 2011)). In the same study, 243 pmol/l (= 70 pg/dl) was estimated to be the lower limit of free testosterone.

14.1.3 Surveillance of testosterone substitution therapy

The physiological effects of testosterone can be used for monitoring the efficacy of testosterone

substitution therapy (Table 14.2). Since therapy aims at replacing the testosterone endogenously lacking, and since physiological serum concentrations are well known, serum testosterone levels also provide a good parameter for therapy surveillance. Guidelines for monitoring testosterone therapy in general were first issued by the World Health Organization (1992), followed by various societies and organizations as summarized in Chapter 18.

14.1.3.1 Behavior and mood

The patient's general well-being is a good parameter to monitor the effectiveness of replacement therapy. Under sufficient testosterone replacement the patient feels physically and mentally active, vigorous, alert and in good spirits; too low testosterone levels will be accompanied by lethargy, inactivity and depressed mood (Burris *et al.* 1992; Wang *et al.* 1996; Zitzmann and Nieschlag 2001) (see also Chapter 5).

14.1.3.2 Sexuality

The presence and frequency of sexual thoughts and fantasies correlate with appropriate testosterone substitution; while loss of libido and sexual desire are a sign of subnormal testosterone values. Spontaneous erections such as those during the morning phase of sleep will not occur if testosterone replacement is inadequate; however, erections due to tactile or visual erotic stimuli may be present even with low testosterone levels. The frequency of ejaculations and sexual intercourse correlate with serum testosterone levels in the normal to subnormal range. Therefore, detailed psychological exploration or a diary on sexual activity and interests are useful adjuncts in assessing testosterone substitution. For objective evaluation of psychosexual effects, weekly questionnaires on sexual thoughts and fantasies, sexual interest and desire, satisfaction with sexuality, frequency of erections and number of morning erections and ejaculations may be used (e.g. Lee *et al.* 2003; Rosen *et al.* 2011). These questionnaires are specifically suited for monitoring substitution therapy and less for diagnosing hypogonadism.

Priapism has been reported to occur in individual cases, mostly at the beginning of testosterone substitution in adult patients as well as in boys with delayed puberty (Endres *et al.* 1987; Zelissen and Stricker 1988; Ruch and Jenny 1989; Arrigo *et al.* 2005; Ichioka *et al.* 2006). This is an extremely rare effect and may have become even rarer since the new testosterone preparations avoid supraphysiological testosterone serum levels. Decreasing the testosterone dose is the rational consequence, but intervention by aspirating blood from the corpora cavernosa may be acutely necessary.

14.1.3.3 Phenotype

Muscles and physical strength grow under testosterone treatment, and the patient develops a more vigorous appearance (e.g. Wittert *et al.* 2003). The increase in lean body mass at the expense of body fat usually results in a decrease of body weight (Rolf *et al.* 2002). The distribution of subcutaneous fat that shows feminine characteristics in hypogonadism (hips, lower abdomen, nates) may change with increasing muscle mass. In particular, testosterone reduces abdominal fat.

The appearance and maintenance of a male sexual hair pattern is a good parameter for monitoring testosterone replacement (see Chapter 7). In particular, beard growth and frequency of shaving can easily be recorded. Hair growth in the upper pubic triangle is an important indicator of sufficient androgen substitution. While women, boys and untreated hypogonadal patients have a straight frontal hairline, androgenization is accompanied by temporal recession of the hairline and – if a predisposition exists – by the development of baldness. The *pattern* of male sexual hair is of greater importance than the *intensity* of hair growth. The AR polymorphism plays a role in male hair growth and pattern (see Chapter 3). A well-substituted patient may have to shave daily. However, if there is no genetic disposition for dense beard growth, additional testosterone will not increase facial hair.

Sebum production correlates with circulating testosterone levels, and hypogonadal men may suffer from dry skin. In an early phase of treatment patients may even complain about the necessity of shampooing more frequently; they have to be informed that this is a part of normal maleness. The occurrence of acne may be a sign of supraphysiological testosterone levels, and the dose should be reduced accordingly.

Gynecomastia may be caused by increased conversion to estradiol during testosterone therapy, especially under testosterone enanthate injections. After initiation of androgen therapy and consequent decrease of estradiol serum levels, gynecomastia usually disappears. If gynecomastia pre-exists due to an increased estradiol/testosterone ratio in hypogonadal

men, it may decrease during adequate testosterone therapy. However, in severe cases mastectomy by an experienced plastic surgeon may be required.

Patients who have not undergone pubertal development will experience voice mutation soon after initiation of testosterone therapy (Akcam *et al.* 2004). During normal pubertal development the voice begins to break when serum testosterone levels reach about 10 nmol/l and SHBG drops (Pedersen *et al.* 1986). Mutation of the voice is very reassuring for the patient and helps him to adjust to his environment by closing the gap between his chronological and biological age. It is specifically important for the patient to be recognized as an adult male on the phone. Once the voice has mutated it is no longer a useful parameter for monitoring replacement therapy since the size of the larynx, the vocal chords and thus the voice achieved will be maintained without requiring further androgens.

In patients who have not gone through puberty, penis growth will be induced by testosterone treatment and normal erectile function will develop. Since penile androgen receptors diminish during puberty, growth will cease even under continued testosterone treatment (Shabsigh 1997; see Chapter 12).

Patients who did not undergo puberty before the onset of hypogonadism may also develop eunuchoidal body proportions because of retarded closure of the epiphyseal lines of the extremities. Testosterone treatment will briefly stimulate growth, but will then lead to closure of the epiphyses and will arrest growth. In these patients, an X-ray of the left hand and distal end of the lower arm should be made before treatment to determine bone age. The epiphyseal closure may be followed by further X-rays during the course of treatment. In addition, body height and arm span – as measured from the tip of the right to the tip of the left middle finger – should be measured until no further growth occurs. Continued growth, in particular of the arm span, indicates inadequate androgen substitution or extremely rare cases of estrogen resistance or aromatase deficiency (see Chapters 8 and 19).

14.1.3.4 Blood pressure and cardiac function

Overdosing androgens, as can be observed during misuse of testosterone and anabolic steroids, may increase blood pressure by increasing blood electrolytes and water retention, leading in extreme cases to edema (see Chapter 25). During effective testosterone substitution therapy in hypogonadal men such side-effects are not observed (e.g. Whitworth *et al.* 1992). To the contrary, systolic and diastolic blood pressure decrease under regular testosterone substitution. Regular blood pressure measurement should be performed during testosterone therapy, especially during inception of treatment when the testosterone dosages have to be adjusted, and in men with additional problems of the heart and kidneys. In patients with severe cardiovascular problems testosterone must be administered very carefully and in low doses (Basaria *et al.* 2010; Aaronson *et al.* 2011; Chapter 11).

14.1.3.5 Serum testosterone

When serum testosterone levels are used to judge the quality of testosterone substitution it is necessary to be aware of the pharmacokinetic profiles of the different testosterone preparations (Chapter 15). Moreover, in longitudinal surveillance of testosterone therapy it is important to use assay systems that strictly undergo internal and external quality control (Chapter 4). Generally, testosterone serum levels should be measured just before the injection of the next dose of long-acting preparations or transdermal application. The time point of the last injection or administration of oral or transdermal testosterone must be recorded to interpret the serum levels measured.

Levels below the lower normal limit at the end of a three-week interval after testosterone enanthate injection should prompt shorter injection frequency of two-week intervals. Conversely, if the levels are in the high physiological range at the end of the injection interval, the dosing intervals may be extended.

When using the im depot preparation of testosterone undecanoate, peak values remain within the normal range. In order to achieve a steady state at the beginning of substitution the second 1000 mg injection is given 6 weeks after the first; further injections follow 10 to 14 weeks later. Individual intervals are determined according to serum testosterone levels, which are measured immediately before the next injection. These determinations are then repeated in yearly intervals. Values that are too high should lead to extension of injection intervals, those that are too low to a shortening of injection intervals (Zitzmann and Nieschlag 2007).

Low serum testosterone levels two to four hours after ingestion of oral testosterone undecanoate should prompt counseling of the patient so that the

capsule is taken together with a meal and testosterone is better absorbed. However, it is difficult to base monitoring of treatment with oral testosterone undecanoate on serum testosterone levels, and other parameters are of more importance if this mode of therapy is chosen.

When transdermal preparations are applied, serum testosterone levels may be measured just before the next dose is administered. Initial measurements, however, are only meaningful after two or three weeks following initiation of therapy, since it takes time until the skin builds up a reservoir and steady state serum levels are reached.

After initiation of testosterone substitution, measuring serum testosterone under the conditions mentioned above is recommendable after 3 to 6 and 12 months, and thereafter annually.

In blood, testosterone is bound to SHBG and other proteins. Only about 2% of testosterone is not bound and is available for biological action of testosterone (free testosterone). Since total testosterone correlates well with free testosterone, separate determination of free testosterone is not necessary for routine monitoring (see also Chapter 4).

14.1.3.6 Serum dihydrotestosterone

Determination of DHT does not play a role in routine monitoring of TRT, but may be of importance in experimental use of testosterone preparations and monitoring biological effects of androgens. Due to the high 5α-reductase activity in skin, transdermal testosterone application is associated with increased serum DHT levels; this applies especially to scrotal application. The DHT adds to the overall androgenicity of the preparation, and a patient receiving transdermal treatment may be well substituted clinically although his serum testosterone does not reflect this. In these cases occasional measurement of serum DHT may be indicated (Kühnert *et al.* 2005; see also Chapter 4).

14.1.3.7 Serum estradiol

In sensitive patients, very high serum testosterone levels, as may occur under testosterone enanthate, may be converted to estrogens and cause gynecomastia. This is an indication to reduce the dose or switch to another testosterone preparation. In this case monitoring serum estradiol levels may explain the clinical findings.

14.1.3.8 Gonadotropins

The determination of LH and FSH plays a key role in establishing the diagnosis of hypogonadotropic (i.e. secondary) or hypergonadotropic (i.e. primary) hypogonadism. However, during surveillance of testosterone therapy they are of less importance. Negative-feedback regulation between hypothalamus, pituitary and testes causes negative correlation between serum testosterone and LH, as well as to some extent to FSH levels in normal men.

In cases with primary hypogonadism (e.g. intact hypothalamic and pituitary function), FSH and in particular LH increase with decreasing testosterone levels and may normalize under testosterone treatment. This is especially the case in patients with acquired anorchia (e.g. due to accidents or iatrogenic castration). However, in the most frequent form of primary hypogonadism, i.e. in patients with Klinefelter syndrome, LH and FSH often do not show significant suppression during testosterone substitution. Moreover, oral or transdermal testosterone may have only little effect on gonadotropins. Therefore LH is not a good indicator of sufficient TRT.

14.1.3.9 Erythropoiesis

Since erythropoiesis is androgen dependent, hypogonadal patients usually present with mild anemia (with values in the female normal range) which normalizes under testosterone treatment. Therefore, hemoglobin, red blood cell count and hematocrit are good parameters for surveillance of replacement therapy. If sufficient stimulation is lacking despite adequate testosterone therapy, lack of iron should be ruled out and treated if necessary. At the beginning of therapy red blood values should be assessed every three months, and later on annually. If too much testosterone is administered, supraphysiological levels of hemoglobin, erythrocytes and hematocrit as a sign of polycythemia can develop, indicating that the testosterone dose should be scaled down (Calof *et al.* 2005). In some cases phlebotomy may be required acutely. The erythropoietic response not only depends on the serum testosterone levels, but also on the age of the patient and androgen receptor polymorphism. Older patients and those with shorter CAG repeats react more sensitively to testosterone (Zitzmann and Nieschlag 2007).

Testosterone has been claimed to potentiate sleep apnea (see Chapter 17); however, only case reports

about the incidence of sleep apnea during testosterone treatment have been published and, paradoxically, hypogonadism has also been cited as a cause of this condition (Luboshitzky *et al.* 2002; Attal and Chanson 2010). Increased hematocrit and increased mass of pharyngeal muscle bulk, as well as neuroendocrine effects of testosterone during therapy were discussed as possible reasons. The development of signs and symptoms of obstructive sleep apnea during testosterone therapy warrants a formal sleep study and treatment with continuous positive airway pressure (CPAP) if necessary. If the patient is unresponsive or cannot tolerate continuous positive airway pressure, the testosterone must be reduced or discontinued.

14.1.3.10 Liver function

The testosterone preparations proposed for testosterone replacement do not have negative side-effects on liver function. Nevertheless, many physicians believe that testosterone may disturb liver function. This impression derives from 17α-methyltestosterone and other 17α-alkylated anabolic steroids which are indeed liver toxic and which should no longer be used in the clinic (see Chapter 25).

Monitoring liver function is of special interest in hypogonadal patients with concomitant diseases that affect liver function, or in patients whose hypogonadism is induced by general diseases. In such cases additional medication is necessary that may influence liver function and thus influence testosterone metabolism, e.g. by increasing SHBG production.

14.1.3.11 Lipid metabolism

Lipid profiles may change under testosterone substitution. Presumed adverse effects such as decreasing high-density lipoprotein (HDL) levels and increasing low-density lipoprotein (LDL) levels have been reported when comparing different treatment modalities (Jockenhövel 1999). However, beneficial effects were also seen, especially in older hypogonadal men, as LDL levels decreased under testosterone substitution and HDL increased. The CAG repeat length of the androgen receptor has a modifying role in the effects on lipid parameters (Zitzmann *et al.* 2003), and pharmacogenetic considerations may in the future influence dose and route of testosterone administration. Currently, it appears sufficient to monitor lipids under testosterone therapy in those patients with grossly abnormal lipid profiles.

14.1.3.12 Prostate

Before initiating testosterone treatment a prostate carcinoma must be excluded. This is done by digital rectal examination (DRE) and PSA determination. Imaging techniques such as transrectal ultrasonography (TRUS) are not considered mandatory, but may add information.

Prostate volume as determined by transrectal ultrasonography is a sensitive end-organ parameter for surveillance. Testosterone substitution therapy increases prostate volume in hypogonadal men, but only to the extent seen in age-matched controls (Behre *et al.* 1994). Prostate volume growth also depends on the AR polymorphism (Zitzmann *et al.* 2003). Prostate-specific antigen increases slightly during therapy but remains within the normal range (Behre *et al.* 1999a; Zitzmann and Nieschlag 2007). Since testosterone therapy must be terminated if a prostate carcinoma occurs and prostate carcinoma is a disease of advanced age, patients above 45 years of age under testosterone treatment should be regularly investigated, first after 3–6 months and 12 months and then at yearly intervals (Wang *et al.* 2008). Measurement of PSA and palpation of the prostate, if possible supported by transrectal ultrasonography, should be performed. As a sign of adequate prostate and seminal vesicle stimulation, ejaculate volume will increase into the normal range.

14.1.3.13 Bone mass

Testosterone replacement therapy in hypogonadal men will increase the low bone mineralization, preventing or reversing osteoporosis and possibly bone fractures (Snyder 1999; Chapter 8). In particular, with respect to bones it is important to use testosterone preparations that can be converted into estrogens since this hormone plays a significant role in bone metabolism (Ohlsson and Vandenput 2009). Bone density should be measured in patients receiving testosterone substitution, prior to treatment and regularly every two years as long as treatment continues. Quantitative computer tomography (QCT) of the lumbar spine provides accurate information; other validated methods are dual photon absorptiometry and dual energy X-ray absorptiometry. Also sonographic measurement of bone density (for example, of the phalangi) provides a useful and inexpensive parameter for monitoring (Zitzmann *et al.* 2002).

14.2 Treatment of delayed puberty in boys

Androgen replacement therapy in male adolescents with constitutional delay of growth and puberty has been shown to be beneficial psychologically as well as physiologically, and should be initiated promptly on diagnosis (de Lange *et al.* 1979; Rosenfeld *et al.* 1982; Albanese and Stanhope 1995; Rogol 2005). Boys with delayed puberty are at risk for not obtaining adequate peak bone mass and for having deficiencies in developing social skills, an impaired body image and low self-esteem. Younger boys with short stature, delayed bone age (at least 10.5 years), and delayed pubertal development in the absence of other endocrinological abnormalities can be treated with 50–100 mg of testosterone enanthate or cypionate im, every four weeks for three months, whereas boys >14 years old may be treated with 250 mg (im, every four weeks for three months). After a three-month "wait and see" period, another course of treatment may be offered if pubertal development does not continue. An increase in testes size is the most important indicator of spontaneous pubertal development (testes volume >3 ml). Overtreatment with testosterone may result in premature closure of the epiphyses of long bones, resulting in reduced adult height. Therefore, treatment of patients who have not yet reached full adult height has to be undertaken carefully.

Low-dose oral testosterone undecanoate has been tested for the treatment of constitutional delay of puberty (Albanese *et al.* 1994; Brown *et al.* 1995). For example, treatment of 11–14-year-old prepubertal boys with 20 mg testosterone undecanoate per day for six months resulted in an increase in growth velocity without advancing bone age and pubertal development (Brown *et al.* 1995). Such "mild" treatment appears to be suited for an early phase when virilization is not yet requested. Transdermal testosterone should also be a useful method to induce puberty. However, experience in a larger series of patients has not yet been reported.

At the beginning of therapy it is often difficult to distinguish between boys with constitutional delay of growth and puberty, who require only temporary androgen replacement, and boys with idiopathic hypogonadotropic hypogonadism, who require lifelong androgen therapy to stimulate puberty and to maintain adult sexual function. However, boys with permanent hypogonadotropic hypogonadism will not have testicular growth induced by androgen therapy. Because pubertal growth is a product of the interaction of growth hormone (GH) and insulin-like growth factor 1 (IGF-1) and the hypothalamic-pituitary-gonadal axis, boys with concomitant GH deficiency will require the simultaneous administration of GH and androgens for the treatment of delayed puberty.

In boys with secondary causes of delayed puberty, development can also be induced by pulsatile GnRH or hCG/hMG respectively. This therapy has the advantage that testicular development is induced simultaneously. However, we prefer to induce initial virilization by testosterone and to stimulate spermatogenesis at a later stage with the more demanding GnRH or gonadotropin therapy.

14.3 Overall stature

The effect of testosterone on epiphyseal closure may be used to treat boys who are dissatisfied with their prospective final overall body height (for review see Drop *et al.* 1998). Treatment has to start before the age of 14. Doses of 500 mg testosterone enanthate have to be administered every two weeks for at least a year to produce effects (Bettendorf *et al.* 1997). This treatment should be reserved for special cases since tall stature is not a disease but rather a cosmetic and psychological problem. However, social and psychological conflicts caused by this condition should not be underestimated. It should also be remembered that testosterone is not registered for this treatment, which has therefore to be considered "experimental." Combining ethinyl estradiol with testosterone injections has no additional height-reducing effect (Decker *et al.* 2002).

An additional reservation comes from the possible effects of such high-dose testosterone treatment at this early age on fertility, the prostate, the cardiovascular system, on bones and other organs. Long-term follow-up of men treated on average 10 years earlier with high-dose testosterone for tall stature revealed no negative effects on sperm parameters and reproductive hormones in comparison to controls (de Waal *et al.* 1995; Lemcke *et al.* 1996; Hendriks *et al.* 2010). Prostate morphology as evaluated by ultrasonography did not show any abnormalities, and serum lipids were not different from the control group. Slightly lower sperm motility was attributable to a higher incidence of varicocele and maldescended testes in the treated men rather than to the treatment as such. Thus it appears that, as far as evaluated, high-dose

treatment has no long-term negative side-effects in these adolescents.

14.4 Micropenis and microphallus

Enlargement of a micropenis or microphallus can be achieved in children by treatment with 25–50 mg of testosterone enanthate or cypionate (im, every three to four weeks for three months; Ishii *et al.* 2004) or with 1.25–5% testosterone cream, 5% DHT cream or 10% testosterone propionate cream (twice daily for three months). High-dose androgen therapy may be necessary to achieve some androgenization in male pseudohermaphroditism caused by 5α-reductase deficiency and certain AR defects.

14.5 Ineffective use of testosterone in male infertility

Since testosterone has been used so effectively in the treatment of endocrine insufficiency of the testes, its use has also been attempted in the treatment of idiopathic male infertility. Testosterone rebound was one of the earliest modalities in this regard. The published success rate in terms of pregnancies varied considerably from center to center, but remained low overall (Charny and Gordon 1978). All studies were uncontrolled trials without placebo and double-blinding, and therefore inconclusive. Testosterone rebound therapy cannot be recommended for treatment of infertility and is no longer practiced.

More recently, testosterone undecanoate has been tested for the treatment of idiopathic male infertility. However, a significant increase in pregnancy rates could not be demonstrated (Pusch 1989; Comhaire *et al.* 1995). When testosterone undecanoate was given combined with tamoxifen and/or hMG, an improvement of semen parameters was observed (Adamopoulos *et al.* 1995; 1997). However, in these studies no pregnancy rates were reported. The therapeutic goal of every infertility treatment should be an increase in pregnancy rates; therefore, studies in which only improved semen parameters are reported, without examining the pregnancy rates, must be considered as inconclusive in terms of infertility treatment. Similarly, after many years of clinical use, no significant effect of mesterolone on pregnancy rates could be demonstrated in an extensive WHO-sponsored multicenter trial (World Health Organization 1989).

Thus, to date testosterone and other androgens have no place in evidence-based treatment of idiopathic male infertility (Kamischke and Nieschlag 1999).

14.6 Contraindications to testosterone treatment

Effects and side-effects of testosterone therapy have been described in detail above. Here the major reasons for not initiating or for interrupting testosterone therapy are briefly summarized.

The major contraindication to testosterone therapy is a *prostate carcinoma*. A patient with an existing prostate carcinoma should not receive testosterone. A carcinoma has to be excluded before starting therapy, and the patient on testosterone should be checked regularly for prostate cancer (digital exploration, PSA, transrectal sonography and biopsy, if necessary). (See also Chapter 13.)

Breast cancer cells often are hormone sensitive, especially estrogen sensitive, and therefore, for reasons of safety, breast cancer is considered a contraindication to testosterone treatment. However, breast cancer is a relatively rare cancer in men and no cases of testosterone substitution and occurrence of breast cancer have been published, as an extended literature search revealed. Thus, this warning cannot be substantiated.

In some countries *sexual offenders* may be or have been treated by castration or antiandrogenic therapy. It would be a serious mistake to administer testosterone to such patients. Relapses and renewed crimes could be the consequence and the responsibility of the prescribing physician. The same holds true for pharmacological androgen deprivation therapy (ADT) using GnRH analogs or antiandrogens, which is currently the preferred therapy for sexual offenders.

Testosterone *suppresses spermatogenesis*: a phenomenon exploited for hormonal male contraception (see Chapter 23). In hypogonadal patients with reduced spermatogenetic function, testosterone administration will also decrease sperm production. Such patients who wish to father children, e.g. by techniques of artificial fertilization, should not receive testosterone substitution therapy, at least not for the time their sperm are necessary for fertilization of eggs. This is of increasing importance as not only residual sperm in patients with secondary hypogonadism but also with Klinefelter syndrome may be

able to fertilize eggs via intracytoplasmatic sperm injection (ICSI) and induce pregnancies (e.g. Lanfranco *et al.* 2004).

14.7 Overall effect of testosterone

Testosterone has many biological functions and, as demonstrated in this chapter, testosterone is a safe medication. There are only very few reasons why testosterone should be withheld from a hypogonadal patient (see Section 14.6). Nevertheless, to date many hypogonadal men still do not receive the benefit of testosterone therapy because they are not properly diagnosed and the therapeutic consequences are not drawn (e.g. Bojesen *et al.* 2003). Some physicians even believe that the shorter life expectancy of men compared to women could be attributed to effects of testosterone. However, large epidemiological studies of healthy men or of patients have demonstrated that men with lower testosterone serum levels have a shorter life expectancy than those with higher testosterone levels (Shores *et al.* 2006; Laughlin *et al.* 2008; Haring *et al.* 2010; Bojesen *et al.* 2011). It remains currently unresolved whether testosterone levels are just an indicator of the general health status or whether there is a causal positive relationship between testosterone levels and longevity. By the same token it remains unresolved today whether testosterone treatment of hypogonadal men may extend or shorten their life expectancy. Without doubt, however, testosterone substitution significantly improves the quality of life of hypogonadal men.

14.8 Key messages

- The primary indications for testosterone therapy are the various forms of male hypogonadism. For substitution, testosterone preparations should be used that can be converted to 5α-dihydrotestosterone (DHT) as well as to estradiol, in order to develop the full spectrum of testosterone action.
- Injectable, oral and transdermal testosterone preparations are available for clinical use. The best preparation is the one that replaces testosterone serum levels at as close to physiological concentrations as possible. This objective is best reached by testosterone gels and by injectable testosterone undecanoate.
- In seven decades of clinical use testosterone has proven to be a very safe medication. No toxic effects are known. The only important contraindication is the presence of a prostate carcinoma which should be excluded before substitution is initiated.
- Testosterone therapy should be monitored by patients' well-being, alertness and sexual activity, by occasional measurement of serum testosterone levels, hemoglobin and hematocrit, by bone density measurements and prostate parameters (rectal examination, PSA and transrectal sonography).
- Testosterone can be used to initiate puberty in boys with constitutional delay of pubertal development. Careful dosing does not lead to premature closure of the epiphysis and reduced height.
- High-dose testosterone treatment in early puberty may prevent expected over-tall stature in boys. Negative long-term effects of this treatment have not become evident to date.
- Testosterone treatment is not indicated in idiopathic male infertility.

14.9 References

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