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Hormone substitution in male hypogonadism

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Abstract

Male hypogonadism is characterised by androgen deficiency and infertility. Hypogonadism can be caused by disorders at the hypothalamic or pituitary level (hypogonadotropic forms) or by testicular dysfunction (hypergonadotropic forms). Testosterone substitution is necessary in all hypogonadal patients, because androgen deficiency causes slight anemia, changes in coagulation parameters, decreased bone density, muscle atrophy, regression of sexual function and alterations in mood and cognitive abilities. Androgen replacement comprises injectable forms of testosterone as well as implants, transdermal systems, sublingual, buccal and oral preparations. Transdermal systems provide the pharmacokinetic modality closest to natural diurnal variations in testosterone levels. New injectable forms of testosterone are currently under clinical evaluation (testosterone undecanoate, testoterone buciclate), allowing extended injection intervals. If patients with hypogonadotropic hypogonadism wish to father a child, spermatogenesis can be initiated and maintained by gonadotropin therapy (conventionally in the form of human chorionic gonadotropin (hCG) and human menopausal gonadotropin (hMG) or, more recently, purified or recombinant follicle stimulating hormone (FSH)). Apart from this option, patients with disorders at the hypothalamic level can be stimulated with pulsatile gonadotropin-releasing hormone (GnRH). Both treatment modalities have to be administered on average for 7–10 months until pregnancy is achieved. In individual cases, treatment may be necessary for up to 46 months. Testosterone treatment is interrupted for the time of GnRH of gonadotropin therapy, but resumed after cessation of this therapy.

Keywords: Male hypogonadism; Testosterone deficiency; Testosterone substitution; Gonadotropins; FSH; LH; GnRH; hCG; hMG

1. Introduction

1.1. Causes for male hypogonadism

Hypogonadism represents a state of impaired testosterone secretion which may be due to testicular failure (hypergonadotropic or primary hypogonadism) or malfunction at the hypothalamic/pituitary level (hypogonadotropic or secondary hypogonadism) and is in most cases associated with infertility. Depending on the localisation of the condition, gonadotropins can be elevated or decreased and accordingly, hypergonadotropic (= primary) hypogonadism is distinguished from hypogonadotropic (= secondary) hypogonadism. Diseases derived from hypothalamic/pituitary malfunction comprise Kallman syndrome and idiopathic hypogonadotropic hypogonadism (IHH), the rare Prader–Labhart–Willi and Laurence–Moon–Biedl syndromes, pituitary insufficiency due to adenoma (including prolactinoma), trauma, surgery in this area or hemochromatosis, constitutional delay of puberty and the Pasqualini syndrome. The hypergonadotropic forms resulting from testicular damage or maldevelopment occur in congenital or acquired anorchia, after chemotherapy or radiation, but also in the Klinefelter syndrome and other chromosomal disorders (i.e. XYY and XX males). Leydig cell tumours, maldescended testes, Noonan's syndrome, gonadal dysgenesis, varicoceles and the Sertoli-cell-only syndrome may be responsible as well. Additionally, enzyme defects in testosterone biosynthesis or luteinising hormone (LH) receptor defects may be causative factors of hypogonadism. Testosterone is often found to be decreased in general diseases such as renal failure, liver cirrhosis and diabetes. Although a target organ resistance may imply the clinical features of hypogonadism, it is not primarily caused by hypogonadism (for classification and

Abbreviations: DHT, dihydrotestosterone; IGF-1, insulin-like growth factor1; PRL, prolactin; PSA, Prostate specific antigen.

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more detailed review of the various forms of hypogonadism see Nieschlag and Behre, 1997).

1.2. Reasons for hormone substitution

Low levels of testosterone lead to severe symptoms, which differ according to the time of onset.

In case of androgen deficiency in early childhood, eunuchoidal proportions, lack of voice mutation, female distribution of secondary hair, anemia, underdeveloped muscles and genitalia can be found, and spermatogenesis and sexual functions are not initiated. If testosterone depletion occurs in later life, after normal virilisation, a distinct decrease in bone mass occurs, decreased bone marrow activity leads to anemia, strength is diminished due to muscle atrophy, and a regression of sexual functions and spermatogenesis is inevitable. Strong evidence exists that behavioural and cognitive aspects are altered, as mood and visual-spatial abilities seem to be impaired in hypogonadism (Janowski et al., 1994; Wang et al., 1996a; Christiansen, 1998; Slabbekoorn et al., 1999).

Pubertas tarda represents an obvious and special area requiring hormonal treatment and testosterone substitution in younger androgen-deficient men has been performed for many years. Treatment of older men with low testosterone levels has long been a topic of discussion, but only recently became the object of controlled clinical studies. There is still some controversy about hypogonadism being related to aging, but indeed its incidence increases with age (Morley et al., 1997; Kaufman and Vermeulen, 1998). Although there is no indication for testosterone medication in senescent men in general, when clinical symptoms require it, hypogonadal older patients should not be denied hormonal substitution (Bhasin et al., 1998; Nieschlag, 1998; von Eckardstein and Nieschlag, 1998). Efforts are being made to find the appropriate treatment modality for such patients.

Achieving fertility in hypogonadal men is only possible in patients with hypogonadotropic hypogonadism and requires gonadotropins or gonadotropin-releasing hormone (GnRH) as part of the therapeutic regime.

1.3. Diagnosis of hypogonadism and fertility assessment

A single serum sample can sufficiently represent the basis of testosterone substitution therapy when taken during morning hours and found to be less than 12 nmol/l (Vermeulen and Verdonck, 1992). Interpretation is complemented by determination of LH levels allowing a distinction between hypo- and hypergonadotropic forms and thus suggesting the location of the disorder. A 0.1-mg GnRH test (injected intravenously, with following assessments of serum gonadotropins and testosterone after 25 and 40 min) can be useful in determining the gonadotropin reserve capacity of the pituitary. If a hypothalamic disorder is suspected during the first GnRH test, and no rise in gonadotropins is observed, a GnRH pump test should be performed (Behre et al., 1997a). Pulsatile treatment with GnRH for 7 days followed by a second GnRH test will distinguish between hypothalamic disease and pituitary insufficiency (Behre et al., 1997a). Haemoglobin and bone density are useful parameters; the possibly reduced size of the prostate is an easily accessible and reliable contributor to the diagnosis of hypogonadism and should be preferably assessed by transrectal ultrasound sonography (Behre et al., 1995a).

Fertility assessment requires at least two semen samples at least 2 weeks apart; analysis should follow WHO guidelines (World Health Organization, 1999).

2. Methods and choices of hormone replacement

Hypogonadism is normally treated with testosterone applied by various methods, but in order to achieve fertility, which is only possible in the hypogonadotropic forms, temporary treatment with gonadotropins (conventionally with human chorionic gonadotropin (hCG)/human menopausal gonadotropin (hMG) or, more recently, with purified urinary follicle stimulating hormone (FSH) or recombinant human FSH) or pulsatile GnRH is required. Once paternity has been achieved, the treatment scheme should switch back to the more convenient and cost-effective testosterone substitution. Information about state of the art forms of hormone treatment in hypogonadal men will be given in following sections.

2.1. Hormone replacement by GnRH or gonadotropins

In hypogonadotropic hypogonadism the origin of the disease influences the choice of treatment to achieve fertility. GnRH substitution is only effective in hypothalamic disorders, a pituitary insufficiency always requires administration of gonadotropins (either the conventional choice of human chorionic gonadotropin and human menopausal gonadotropin, or purified urinary FSH, or more recently, recombinant human FSH).

FSH plays a pivotal role in the initiation and maintenance of spermatogenesis. The induction of proliferation of Sertoli cells and spermatogonia depends on this gonadotropin (Nieschlag et al., 1999a). Recently a case was reported in which a patient with a mutation in the FSHβ-chain was infertile and suffered from hypogonadism (Philip et al., 1998).

Concerning maintenance of spermatogenesis by FSH, several experiments in monkeys with long-term immunisation against FSH induced testicular regression and

oligo- or azoospermia (Mougdal and Sairam, 1998). In the cases of oligozoospermia the few sperm left were probably functionally impaired, as these monkeys were infertile in mating tests.

Similarly, a recently conducted study in India with human volunteers receiving an FSH vaccine showed altered parameters of sperm quality such as acrosome content and chromatin condensation. A marginal suppression of sperm counts was achieved (around 30–65%) after the short duration of four spermatogenic cycles, indicating that elimination of FSH not only causes quantitative, but possibly also qualitative damage of spermatogenesis (Mougdal et al., 1997).

In the setting of a contraceptive trial using a testosterone ester, complete azoospermia was reached only in those subjects whose serum FSH levels were suppressed below the lower limit of the normal range (Behre et al., 1995b).

The role of FSH is demonstrated impressively by the example of a hypophysectomised patient, who had full spermatogenesis and was still fertile due to an activating mutation of the FSH receptor which was able to induce receptor activity (cAMP production) without FSH stimulation (Gromoll et al., 1996).

For completely normal spermatogenesis, FSH and testosterone are important, and the intratesticular location of testosterone is also crucial. Thus for treating infertility in hypogonadal men, there is a need for high intratesticular testosterone levels to initiate spermatogenesis. This was demonstrated by treating men with hypogonadotropic hypogonadism with purified FSH and testosterone and comparing its effectiveness to hCG/hMG therapy. The latter was able to induce spermatogenesis while the FSH/testosterone regimen failed to do so (Schaison et al., 1993).

Following hormonal treatment to achieve fertility in hypogonadotropic hypogonadal men, usually sperm counts below the lower limit of the normal range are seen. This does not preclude fertility, as has been demonstrated in 24 men with IHH who proved fertile after gonadotropin therapy. Seventy-one percent of a total of 40 initiated pregnancies were conceived with sperm concentrations ranging from 1 to 20×10^6/ml (Burris et al., 1988b). Confirming results were seen in 42 cases of fertility treatment in hypogonadotropic hypogonadal men using pulsatile GnRH therapy or the hCG/hMG regimen (Büchter et al., 1998).

Initial testicular volume allows prediction of the necessary duration of therapy until sperm first appear in the ejaculate. Spermatogenesis can be induced even in patients with a very small testicular volume (of less than 3 ml), but this may require treatment for 18–24 months (Burris et al., 1988a; Büchter et al., 1998). During therapy, testicular volume can be monitored carefully by ultrasound sonography, in order to detect subtle increases, which precede the first appearance of sperm.

A review of 42 patients showed that previous maldescent (uni- or bilateral) hampers spermatogenesis and requires a longer course of treatment, but does not preclude patients from gaining fertility. This is especially the case in unilateral maldescent, but there are also reports of patients with bilateral cryptorchidism having been treated successfully. The group comprising all patients with unilateral maldescent required 5 months of treatment until induction of spermatogenesis (1–16 months); 13 months (12–22 months) was the average time for patients with bilateral maldescent. In comparison all patients with no history of maldescent needed 4.5 months of treatment (2–18 months; Büchter et al., 1998). This is in accordance with other studies (Saal et al., 1991; Delemarre-van de Waal, 1993; Jones and Darne, 1993).

Since treatment may be required up to for 24 months, it is strongly recommended that patients with hypogonadotropic hypogonadism try to induce spermatogenesis even prior to the immediate desire for paternity. In repeatedly treated patients, stimulation of spermatogenesis tended to be faster, leading to a reduced time to pregnancy (Büchter et al., 1998).

2.1.1. Pulsatile GnRH therapy

Treatment with GnRH requires subcutaneous pulsatile application using a portable pump and a butterfly needle placed in the abdominal wall and changed every 2 days. The dose ranges from 5 to 20 μg/120 min, or 100–400 ng/kg per 120 min. Low-dose pulsatile GnRH therapy (2 μg/150 min) may not elicit a sufficient pituitary response, reflecting different degrees of pituitary maturation (Happ et al., 1985). In most cases the induction of spermatogenesis is evidenced by the appearance of sperm in the ejaculate. Therapy lasts on average 4 months, as shown in six of seven GnRH therapy cycles in patients with idiopathic hypogonadotropic hypogonadism or Kallman syndrome (Büchter et al., 1998). Sperm counts were below the normal range $1.2–15.3 \times 10^6$/ml. Similar results have been demonstrated in other studies (Liu et al., 1988; Delemarre-van de Waal, 1993; Schopohl, 1993). Despite low sperm counts, pregnancies can be achieved, the duration until conception being on average 6–7 months.

Under treatment testicular size will increase significantly, as demonstrated in the above mentioned patients where the initial mean size of 6.8 ± 2.2 ml rose to 14.9 ± 3.2 ml after 5–12 months of treatment with pulsatile GnRH (Büchter et al., 1998).

When pulsatile GnRH treatment fails, mutation of the GnRH receptor gene can be the cause. These defects have been recently described and are probably transmitted as an autosomal recessive trait. A variable degree of hypogonadism in an affected kindred was seen: a male showed no response to pulsatile adminis-

tration of GnRH, which was effective in his two sisters, all showing clinical patterns of hypogonadotropic hypogonadism (de Roux et al., 1999).

Another cause for failure of pulsatile GnRH treatment was observed in a patient who formed anti-GnRH antibodies during intravenous administration. This was associated with deterioration of testosterone and gonadotropin levels (Blumenfeld et al., 1988).

2.1.2. Gonadotropin therapy

In order to achieve fertility in cases of pituitary lesions or GnRH receptor gene defects, the regimens using gonadotropins must be applied, but they are also an option in hypothalamic disorders. Conventional therapy uses the hCG and hMG, both purified extractions from urine. Recently highly purified urinary FSH and recombinant human FSH have been introduced; the recombinant form of LH is currently being tested.

2.1.2.1. Treatment with hCG/hMG. As the subunits of hCG and LH are structurally very similar, they act on the same receptor on Leydig cells. This effect is used to substitute LH by purified urinary hCG from women.

Human menopausal gonadotropin contains both LH- and FSH-activity. However, a dose that provides adequate FSH-activity does not maintain Leydig cell function because the LH-activity is low. Thus a combination with hCG is required to achieve fertility. Ninety-five percent of hMG consists of co-purified proteins that lack LH or FSH activity and is believed to cause the hypersensitivity reactions occasionally observed under hMG therapy, but not under highly purified hMG or recombinant FSH (Redfearn et al., 1995; Albano et al., 1996; Biffoni et al., 1998). HCG may also induce antibody formation (Nieschlag et al., 1982), which only in rare cases may neutralise hCG bioactivity (Sokol et al., 1981; Claustrat et al., 1983; Thau et al., 1988). Contraceptive trials in women using the effect of antibody formation against hCG after vaccination (with preparations based on the β subunit of hCG; Deshmukh et al., 1994) have shown that pregnancy can be prevented at and above 50 ng/ml antibody titers (Singh et al., 1998).

Therapy is initiated by administration of hCG alone, which is given intramuscularly or subcutaneously. The usual dose is 1000–2500 I.U. applied twice per week (Monday and Friday) for a period of 8–12 weeks; adjustments have to be made to achieve testosterone levels within the normal range. In some cases by then sperm can be found in the ejaculate, due to residual FSH secretion (Finkel et al., 1985; Burris et al., 1988a; Vicari et al., 1992).

Following the induction phase, hMG is administered intramuscularly or subcutaneously at a dose of 75–150 I.U. thrice weekly (Monday, Wednesday, Friday). Sometimes it may be necessary to reduce the hCG dose due to increasing testosterone levels or development of gynecomastia caused by increased levels of testosterone which are metabolised to estradiol.

A review of nine patients with IHH, nine patients with Kallmann syndrome (group A) and 21 patients with hypopituitarism (group B) treated with this regimen showed appearance of first sperm in the ejaculate after an average period of 6 months (1–18 months) in group A, and 4 months (2–16 months) in group B. Sperm concentrations were 1.2×10^6/ml ($0.1–9.0 \times 10^6$/ml) in group A, and 8.1×10^6/ml ($0.1–180 \times 10^6$/ml) in group B. As mentioned above, duration of therapy depends on the initial testicular size and the patients' history of uni- or bilateral maldescent. Pregnancies were induced in five of ten patients belonging to group A (time to pregnancy on average 8 months), and in 17 of 21 patients of group B (time to pregnancy on average 10 months; Table 1). Testicular size increased from 4.4 ± 2.86 to 15.3 ± 7.4 ml (group A), and from 14.0 ± 8.7 to 28.3 ± 10.9 ml (group B; Büchter et al., 1998). This is in concordance with previously reported results (Liu et al., 1988; Schopohl, 1993).

2.1.2.2. Treatment with hCG/highly purified urinary human FSH (urinary-hFSH). Improved purification methods have provided highly purified urinary FSH with enhanced specific activity in comparison to hMG (10 000 I.U./mg of protein vs. 150 I.U./mg of protein for hMG). A study including 28 men with hypogonadotropic hypogonadism examined the effects of hCG 2000 I.U. twice weekly for 3–6 months followed by 18 months of additional subcutaneous administration of highly purified urinary FSH. Twenty-five patients achieved spermatogenesis, 18 of them with a sperm density of more than 1.5×10^6/ml. The median time to initiation of spermatogenesis as judged from the appearance of sperm in the ejaculate was 9 months. Mean testicular volume increased from 3.6 ± 1.7 to 10.5 ± 4.1 ml. The partner of one patient seeking fertility conceived a child. The effectiveness was comparable to regimens using hCG/hMG (European Metrodin HP Study Group, 1998).

Confirming results were seen in 14 prepubertal males with isolated hypogonadotropic hypogonadism or panhypopituitarism; complete virilisation was achieved in all patients; in seven of eight patients willing to provide ejaculates spermatogenesis was achieved (Barrio et al., 1999).

The subcutaneous form of application makes self-administration feasible: in 60 men with different forms of hypogonadotropic hypogonadism (16 with Kallmann syndrome, 19 with IHH, 25 with hypopituitarism) highly purified urinary FSH (150 I.U. thrice/week) and hCG (2500 I.U. twice/week) were tested for at least 6 months in a self-administration regimen. Results were comparable to other studies and the treatment was well

Table 1
Results of different treatment modalities to achieve fertility in hypogonadotropic hypogonadism[a]

Disorder and treatment	Time to first appearance of sperm in ejaculate		Time to pregnancy		Testicular volume		
	Induction of spermatogenesis in no. of courses	Months (average and range)	Induction of pregnancy in no. of courses	Months (average and range)	*n*	Pretreatment (ml ± S.D.)	Posttreatment (ml ± S.D.)
IHH, KalS/pulsatile GnRH	6/7	4 (2–22)	4/5	6.5 (3–21)	6	6.8 ± 2.2	14.9 ± 3.2
IHH, KalS/hCG/hMG	18/20	6 (1–18)	5/10	8 (1–15)	18	4.4 ± 2.86	15.3 ± 7.4
Pituitary disorder/hCG/hMG	30/30	4 (2–16)	17/21	10 (2–46)	21	14.0 ± 8.7	28.3 ± 10.9

[a] Some patients received repeated treatment courses (data from Büchter et al., 1998).

tolerated, showing efficacy and safety of this combined treatment (Burgues and Calderon, 1997).

2.1.2.3. Treatment with hCG/recombinant human FSH (r-hFSH). r-hFSH has advantages over urinary preparations in terms of purity, specific activity, consistent composition and constant supply. Isolated genes from human fetal liver cells were inserted via vectors into a Chinese hamster ovary cell line, resulting in expression of biologically active human FSH (Recombinant Human FSH Product Development Group, 1998). Multiple-dose pharmokinetics showed an elimination half-life of 48 ± 5 h and proved that serum FSH is increased in a dose-proportional fashion. No intrinsic LH activity was detected (Mannaerts et al., 1996). Nevertheless, it has been demonstrated that r-hFSH increases testosterone concentration in spermatic venous blood. The testosterone production described in Leydig cells is assumed to be increased by a Sertoli cell-released nonsteroid factor (Levalle et al., 1998).

Early case reports suggested its effectiveness in inducing spermatogenesis in hypogonadotropic hypogonadism (Kliesch et al., 1995). A study including ten men with hypogonadotropic hypogonadism due to hypothalamic or pituitary disorders provided data concerning the combined therapy with recombinant FSH (150 I.U. s.c. thrice/week) and hCG (2000 I.U. 2–3 times/week). Eight men commenced r-hFSH treatment and seven of these initiated spermatogenesis at a median of 6 months. Five achieved a sperm output of more than 1.5×10^6/ml. Mean testicular volume increased by 4.2 ml. Three pregnancies were achieved during FSH treatment. Its efficacy is comparable to urinary FSH in restoring normal fertility in men with gonadotropin deficiency (Liu et al., 1999).

In women, clinical experience showed recombinant FSH to be more effective in stimulating ovarian follicle growth than urinary gonadotropins (Recombinant Human FSH Product Development Group, 1998).

2.1.2.4. Recombinant human LH (r-hLH). Similarly r-hLH is likely to replace hCG in the future in clinical use for therapy of male hypogonadotropic hypogonadism, for the recombinant hormones are considered safer and more reliable than their extracted forms.

Exposing immature porcine Leydig cells to r-hLH for different time periods showed several precursors of testosterone being converted at a significantly increased rate after 24 h. Moreover the expression of several genes encoding proteins involved in testosterone synthesis was increased. Despite this, a marked down regulation of the LH/hCG receptor mRNA was described (Lejeune et al., 1998).

In women, recombinant human LH has already been tested as an additional medication in controlled ovarian stimulation in cases of low LH concentrations and has proven to be successful in cases of previous stimulation failure (Laml et al., 1999).

2.1.3. Comparison between therapy with GnRH or gonadotropins

There is still uncertainty about the optimal treatment modality in patients with hypogonadotropic hypogonadism caused by disorders at the hypothalamic level. A recent review reported 42 cases of men with hypogonadotropic hypogonadism treated for infertility, comprising 24 patients with IHH or Kallmann syndrome. Six of these received pulsatile GnRH treatment, the other 18 the conventional hCG/hMG regimen. No statistically significant differences in terms of first appearance of sperm in the ejaculate or time to pregnancy were seen (Table 1). Nor was the increment of testicular size significantly different (Büchter et al., 1998).

Another study with 36 patients with disorders at the hypothalamic level (IHH or Kallmann syndrome), divided into groups of 18, reported no significant difference in effectiveness with respect to sperm counts. In GnRH therapy increment of testicular volume occurred more rapidly and was significantly more pronounced than under the gonadotropin regimen. Five patients with the latter therapy developed gynecomastia, probably due to the significantly higher testosterone concentrations in that group (Schopohl, 1993).

A 2-year comparison including 16 patients showed no advantage of either therapy concerning acceleration and/or enhancement of testicular growth, onset of spermatogenesis or increment of sperm output (Liu et al., 1988).

2.1.4. Application of recombinant human growth hormone (r-hGH) in male hypogonadotropic hypogonadism

The GH/IGF-1 axis was studied in 15 azoospermic patients with hypergonadotropic (eight) and hypogonadotropic (seven) hypogonadism, while ten healthy men served as controls. The hypergonadotropic patients received testosterone treatment for androgenisation, the hypogonadotropic men gonadotropin therapy for induction of spermatogenesis. Before and after treatment basal serum levels of IGF-1 and the GH-response to clonidine were not affected (Carani et al., 1999b).

Accordingly, the treatment with r-hGH of 11 adult males following neurosurgery because of pituitary lesions induced no significant change in sperm count and motility. Baseline testosterone was not altered, but hCG stimulation led to significantly increased levels of testosterone. Seminal plasma volume was increased as well (Carani et al., 1999a).

We recently investigated the effects of human growth hormone on testicular function in a non-human primate model. Cynomolgus monkeys were treated for 1

year with r-hGH being given daily as subcutaneous injections of various doses. Spermatogenesis, as judged from semen analysis, testicular volume and testicular morphology did not change; the only alterations observed were a dose-dependent increase of IGF-1 and decreasing PRL levels (Sjogren et al., 1999).

In summary, there seems to be an effect on Leydig cell function, but spermatogenesis and spermfunction are not altered by administration of r-hGH.

Prostate development under high GH levels has been examined in 46 acromegalic patients and 30 age-matched controls. Benign prostate hyperplasia was found in 58% of the acromegalics and 26.6% of the controls. Structural abnormalities, which included calcifications, nodules, cysts and vesicle inflammation were significantly increased in patients in comparison to controls. GH and IGF-1 levels were increased in active acromegalic patients, but not in the treated ones. Reduced testosterone levels were found in patients with high GH levels, which could be explained by suppressed LH levels due to the pituitary lesion caused by the disease. No clinical, transrectal ultrasoundsonography or cytological evidence of prostate cancer was detected, neither in patients nor controls (Colao et al., 1999).

Although the model of acromegaly is not completely transferable to substitution therapy in hypogonadism, it is demonstrated that a chronic excess of GH can cause prostate overgrowth, which is a limiting factor of possible therapy.

Table 2
Modalities of current testosterone substitution

Preparation	Application	Dosage
Testosterone undecanoate	Orally, with meals	2–4 capsules of 40 mg/day
Testosterone enanthate	Intramuscular injection	200–250 mg every 2–3 weeks
Testosterone cypionate	Intramuscular injection	200 mg every 2 weeks
Transdermal testosterone patch	Scrotal skin (i.e. Testoderm®)	1 membrane per day
Transdermal testosterone patch	Non-scrotal skin (i.e. Androderm®)	1 or 2 patches per day
Testosterone implants	Implantation under abdominal skin	3–6 implants à 200mg per 6 months
Testosterone gel	Transdermal application	Under development
Buccal testosterone	Absorption through buccal mucosa	Under development
Testosterone cyclodextrin	Sublingual	Under development
Testosterone undecanoate	Intramuscular injection	Under development
Testosterone microspheres	Intramuscular injection	Under development
Testosterone buciclate	Intramuscular injection	Under development

2.1.5. Hormonal treatment of normogonadotropic oligoasthenotheratozoospermia

Since GnRH and the different gonadotropins have proven their benefit in induction of spermatogenesis in hypogonadotropic hypogonadism, the application of these substances was tried in idiopathic male infertility.

While the application of pulsatile GnRH resulted in a decrease in FSH levels, no effect on primary reproductive parameters was seen. There is no evidence for a benefit of this treatment modality (Bals-Pratsch et al., 1988, 1989). One randomised, controlled study using hCG/hMG for treatment of normogonadotropic oligoasthenotheratozoospermia provided no positive information with respect to sperm parameters or pregnancy rates (Knuth et al., 1987).

Similarly, recently a randomised, double-blind, controlled clinical trial using recombinant human FSH (daily subcutaneous injections of 150 I.U. r-hFSH) for treatment of idiopathic male infertility in 67 patients showed no significant changes in semen parameters apart from an increase in sperm motility in the placebo group and in sperm DNA condensation in the treated group. Testicular volume was increased in the treated group compared to the placebo group. However, there was no increase in pregnancy rate in the treatment group (Kamischke et al., 1998).

On the basis of controlled studies, treatment of idiopathic infertility in normogonadotropic men with r-hFSH and other gonadotropins or pulsatile GnRH cannot be recommended (Kamischke and Nieschlag, 1999).

2.2. Testosterone substitution

Nowadays oral, injectable, transdermal and implantable testosterone preparations are available for clinical use, each with its unique pharmacokinetic profile. To date there is no evidence that would justify abandoning the WHO/NIH/FDA consensus of 1990: 'The consensus view was that the major goal of therapy is to replace testosterone levels at as close to physiologic concentrations as possible' (World Health Organization et al., 1999). With the exception of transdermal testosterone application, none of the testosterone preparations available to date can fully achieve this goal (Table 2 summarises current testosterone substitution modalities).

2.2.1. Obsolete and discontinued preparations

Since free, unesterified testosterone is absorbed well after ingestion but inactivated due to the 'first-pass-effect' in the liver, results varied following oral ingestion, depending on hepatocyte function which differs in men, women, adolescent boys or patients with liver cirrhosis

(Gluud et al., 1993; Nieschlag and Behre, 1998). One preparation of free testosterone led to unreliable rates of absorption (Daggett et al., 1978). Subsequent attempts to render the steroid molecule orally effective led to changes in the 17α-position. These substances, 17α-methyltestosterone and fluoxymesterone, were shown to be toxic to hepatocytes: associations with liver tumours were described. Use of these substances has been terminated in the EU, but they are still available in some other countries.

Mesterolone, resembling 5α-dihydrotestosterone, is protected from fast metabolism in the liver and can be administered orally. It cannot be metabolised to estrogens, thus lacking some of normal testosterone's abilities. Its ability to suppress gonadotropin production is limited. Considered only a weak androgen, it is not suitable for therapy in hypogonadism (Nieschlag and Behre 1998).

To avoid first-pass effects, testosterone preparations for rectal application were developed. One suppository contained 40 mg of testosterone and application resulted in an immediate and steep increase of testosterone serum levels, an effect lasting for about 4 h. To obtain effective serum levels, administration of three suppositories per day was required; this practice did not gain much popularity (Nieschlag et al., 1976).

First-pass effects can also be avoided by nasal application of testosterone. This modality provided unreliable absorption patterns and serum peaks were short-lived. Thus nasal application of testosterone seemed unsuitable for long-term therapy and development did not pass the experimental state (Danner and Frick, 1980).

2.2.2. Oral application with intestinal absorption

Though mesterolone sometimes is used in the setting of a clinical trial (Jockenhövel et al., 1999), the established domain of oral testosterone substitution lies with testosterone undecanoate. Its route of absorption follows the lymphatic pathways due to esterification with a long aliphatic chain; hence liver passage is avoided (Coert et al., 1975). Capsules contain 40 mg, and though yielding wide fluctuations in testosterone serum levels (Nieschlag and Behre, 1998), oral treatment of hypogonadism can be achieved by administration of two to four capsules. Pharmacokinetics were determined in several studies, resulting in values of high intra- and interindividual variability in serum concentrations (for review Behre and Nieschlag, 1998). This preparation is best suited as a supplement to reduced but still present endogenous androgen levels, since it does not fully suppress the pituitary (Nieschlag, 1998). Long-term use has proven it to be safe, as demonstrated in a 10-year observation study (Gooren, 1994).

2.2.3. Sublingual application

Sublingual application were tested with a 2-hydroxypropyl-β-cyclodextrin as inclusion complex for the hydrophobic testosterone molecule. Rapid increase in testosterone serum levels were seen, unfortunately declining to below normal range after 2 h (Stuenkel et al., 1991). Unless serum levels can be maintained at constant levels, this interesting approach has to be considered of no further benefit (Wang et al., 1996b).

2.2.4. Buccal application

As transbuccal administration of drugs represents a comfortable route of application, a testosterone preparation was studied in a randomised, controlled, double-blind design. Thirteen men with testosterone levels below 250 ng/dl participated and were randomised to either take an active buccal tablet containing 10 mg of testosterone ($n = 7$) or a buccal placebo preparation ($n = 6$). The groups were matched for age and type of hypogonadism (three hypergonadotropic men in each group, the others with disorders at the central level). Pharmacokinetics showed peak serum levels of 2688 ± 147 ng/dl, which returned to baseline within 4–6 h. Similar results were described for testosterone metabolites. After 8 weeks of treatment, a significant difference to the placebo group was seen in regard to nocturnal penile tumescence. A subjective assessment via questionnaire yielded confirming results concerning improved sexual functions. The results were comparable to those seen under testosterone enanthate therapy. Thus sexual functions were improved with a well-tolerated treatment modality with favourable pharmacokinetics (Dobs et al., 1998).

2.2.5. Intramuscular application

Since free testosterone is degraded with a half-life of only 10 min, esterification led to more suitable forms of injectable preparations. While some substances have been used for many years, others with more favourable absorption profiles are under clinical evaluation. Currently available testosterone esters initially produce supraphysiological testosterone levels, slowly declining to even pathologically low levels before the next injection. These changes are often noticed by patients in terms of marked swings in vigour, sexual activity and emotional stability (Nieschlag and Behre, 1998).

2.2.5.1. Testosterone enanthate (TE). TE is one of the most common preparations for testosterone substitution. This substance has a terminal half-life of 4.5 days; maximum concentrations are reached after 10 h following a single injection of 250 mg (Nieschlag et al., 1976). Multiple-dose pharmacokinetics reveal an optimal injection interval of 2–3 weeks at a dose of 200–250 mg, but peak and trough values still continue above/below the normal range (Behre and Nieschlag, 1998). In

healthy men, this dose at weekly intervals led to constant supraphysiological levels between 40 and 80 nmol/l, as contraceptive studies have shown (Anderson and Wu, 1996).

2.2.5.2. Testosterone propionate. This substance has a terminal half-life of only 19 h; after a single injection of 50 mg the maximum concentration was reached after 14 h (Nieschlag et al., 1976).

It is obvious that this substance requires more frequent injections: multiple-dose pharmacokinetics reveal optimal intervals of 2–3 days, but fluctuations below normal range values persist (Behre and Nieschlag, 1998). Judging by these data, the substance is not suitable for long-term treatment of hypogonadism.

2.2.5.3. Testosterone cypionate and testosterone cyclohexanecarboxylate. These substances resemble the pharmacokinetic properties of testosterone enanthate (Schulte-Beerbühl and Nieschlag, 1980; Schürmeyer and Nieschlag, 1984). They do not provide an advantage over the enanthate ester. The recommended dose for testosterone cypionate is 200 mg every 2 weeks according to a trial in 11 hypogonadal patients (Nankin, 1987).

2.2.5.4. Testosterone undecanoate. While already in use as oral preparation, an injectable form with prolonged duration of action was described in a Chinese study (Wang, 1991). Comparison of pharmacokinetics with testosterone enanthate in orchiectomised cynomolgus monkeys revealed a significantly longer half-life (Partsch et al., 1995). Phase I studies comparing different concentrations and solutions (8 ml, divided into 2×4 ml — injections, of tea seed oil with 125 mg/ml and 4 ml castor oil with 250 mg/ml) demonstrated a longer half-life of the latter preparation (33.9 ± 4.9 vs. 20.9 ± 6.0 days, mean $\pm$ S.E.M.). Thus a smaller injection volume can be achieved with the dose of 1000 mg that led to maximal concentrations of 19.3 ± 2.1 nmol/l after 11.4 ± 1.5 days (Behre et al., 1999a). Terminal half-life was determined as 33.9 ± 4.9 days. The optimal injection interval was set between 6 and 8 weeks. A recent study with four injections of 1000 mg testosterone undecanoate in 4 ml castor oil at 6-week intervals in 13 hypogonadal men (eight with the primary, five with the secondary form) represented a well-tolerated treatment with testosterone serum levels that were never found below lower limits of normal and only briefly exceeded upper limits of normal after the third and fourth injections (40.8 ± 3.8 nmol/l). The intervals may even be extended to 12 weeks (Nieschlag et al., 1999b).

2.2.5.5. Testosterone buciclate. First results in cynomolgus monkeys showed a rather favourable pharmacokinetic profile of this long-acting, slow-release preparation (Weinbauer et al., 1986). Further clinical studies showed a maximum concentration after 9 weeks of 13.1 ± 1.8 nmol/l, the half-life being about 30 days. This injection of 1000 mg testosterone buciclate maintained testosterone serum levels within the normal range up to week 16 (Behre et al., 1995b). This substance seems to be very suitable for long-term testosterone substitution and is under further development.

2.2.5.6. Testosterone ester combinations. Mixtures of testosterone esters (i.e. Testoviron Depot® 50/100: testosterone propionate 20/25 mg and testosterone enanthate 55/110 mg; Sustanon® 250: testosterone propionate 30 mg, testosterone phenylpropionate 60 mg, testosterone isocaproate 60 mg and testosterone decanoate 100 mg) designed to act synergistically due to different profiles have been shown to increase the undesired initial peak even further and not to follow zero-order kinetics. Fluctuation is much higher than when testosterone enanthate is applied alone. For treatment of male hypogonadism there seems to be no advantage over single preparations (Behre and Nieschlag 1998).

2.2.5.7. Testosterone microspheres. Biodegradable microspheres may present a vehicle of desirable release kinetics. The latest study provided data of approximated zero-order kinetics over the first 10 weeks after injection of 630 mg of microencapsulated testosterone in ten hypogonadal men. An eugonadal range was reached quickly and maintained for about 75 days (Bhasin et al., 1996). Probably because of problems of stability, no further development has been achieved since then.

2.2.6. Subdermal testosterone implants

Testosterone pellet implantation was among the first modalities employed for clinical use and reaches back to 1937. Modern pellets are produced by high-temperature moulding and are available in two sizes, containing 100 or 200 mg of crystalline steroid, with a length of 6 or 12 mm and a common diameter of 4.5 mm (Handelsman, 1998). Implanted under sterile conditions by a tunnelling technique using a trocar, they remain under the skin of the lower abdominal wall; other possible sites are upper thighs, deltoid or gluteal muscles. Absorption follows via erosion from the pellets' surface.

Pharmacokinetics were studied in three different regimens (6×100 mg, 6×200 mg, 3×200 mg) administered to 43 androgen-deficient men (22 hypergonadotropic, 21 hypogonadotropic) for at least 6 months. Testosterone levels peaked at the first month

and were maintained at eugonadal levels for 4–6 months, depending on dose. Absorption from both types of pellets approximately followed zero-order kinetics (Handelsman et al., 1990). Another study with 6×200 mg crystalline, fused testosterone reported an initial burst release with peak concentrations about 50 nmol/l on the first day, following approximated zero-order kinetics, a stable plateau phase lasted for 63 days; terminal half-time was calculated at 71 days, and eugonadal levels could be maintained for about 180 days (Jockenhövel et al., 1996).

A comparison between intramuscular injections of 250 mg mixed testosterone esters at 2-weekly intervals, oral testosterone undecanoate (120 mg/day) and subcutaneous pellets (6×100 mg) in a prospective, randomised, cross-over design indicated a constant elevation of testosterone in the pellet-treated patients that lasted for 4 months, whereas marked fluctuations were seen in the injection group. Oral testosterone undecanoate provided most variable plasma levels (Conway et al., 1988). A similar setting, including (ineffective) oral mesterolone, testosterone enanthate (250 mg every 3 weeks) and 1200 mg subcutaneously implanted crystalline testosterone confirmed these results (Jockenhövel et al., 1999).

A review of 13 years of experience in subdermal testosterone implantation in 221 men showed limited adverse local effects (11% of total 973 consecutive implants) such as extrusion, bleeding and inflammations/infections. Effects were related to work activity and occurred more often in thinner men. Palpable subdermal fibrosis is uncommon (Handelsman et al., 1997). Overall, pharmacokinetic profiles resemble those of intramuscular injected testosterone, but the prolonged decrease makes changes undetectable to patients.

Since surgical removal is inconvenient, pellets should be applied to patients in whom the benefit of testosterone substitution has already been demonstrated by shorter-acting regimens. In cases of foreseeable adverse effects caused by testosterone (see below), implants should not be used. This may especially apply to older men with the risk of prostate disease (Nieschlag, 1998). Notwithstanding, subdermal implants offer a long-acting, cost-effective method of testosterone substitution, often preferred by patients to other methods. To date they are commercially available in the United Kingdom, South Africa and Australia.

2.2.7. Transdermal testosterone application

Delivering testosterone through the intact skin has become feasible during recent years. It can be administered either through scrotal or non-genital skin (Bhasin et al., 1998). Delivering the unmodified hormone through the skin avoids first-pass effects and mimics the circadian rhythm of testosterone secretion, a factor previously not achievable (Atkinson et al., 1998). Since differences in transmission of the substance depend on the application site (absorption through non-genital skin is 40 times less effective than through scrotal epidermis), preparations have to be designed differently.

2.2.7.1. Scrotal patches. Already tested in the 1980s (Bals-Pratsch et al., 1986, 1988), this application form is available as Testoderm®. It consists of a film containing 10 or 15 mg natural testosterone, is applied daily and delivers the substance at a total dose of 4–6 mg/day. The patch is rather thin (0.14 mm) and is worn for 22–24 h. Advantages of this preparation are self-administration and the possibility of removing the androgen source in case of an adverse event. This applies to the non-scrotal patches as well. Patients have to shave scrotal hair to enable the patch to adhere properly.

Pharmacokinetics properties are as follows: initial rise to maximum 2–4 h after application, maintaining levels in the medium range for the designed application period. After removal, testosterone levels quickly return to baseline values (Atkinson et al., 1998).

A study of long-term substitution via this system in 11 hypogonadal showed testosterone levels being maintained in the eugonadal range throughout treatment, which lasted for 7–10 years. Bone density could be kept at status quo or slightly increased. Prostate volumes slightly increased within the normal range, PSA levels remaining within normal range. Kinetic release profiles were considered to be excellently adjusted to WHO requirements of testosterone substitution (Behre et al., 1999b). Since there are special principles to be followed in testosterone substitution in older men, such as preferring the natural substance, aiming at physiological hormone levels, and the opportunity of ceasing treatment immediately (due to possible development of prostatic disease), transdermal application represents an adequate treatment modality for this age group (Nieschlag, 1998).

2.2.7.2. Non-scrotal transdermal application systems. The available system for non-scrotal transdermal application of testosterone is marketed as Andropatch® or Androderm®. Most patients require 2×2.5 mg patches or 1×5 mg patches, which are bioequivalent (Meikle et al., 1997). During 24 h of 2×2.5 mg patch application, the cumulative input of testosterone was observed to be 5.48 ± 2.48 mg, 60% being delivered during the first 12 h, 40% during the next 12 h (Meikle et al., 1996). To imitate natural secretion profiles, it is recommended to apply the patch at 22:00 h, since maximal concentrations are reached after ca. 8 h. The usual sites of application are the back, the abdomen, the upper arms or thighs.

In 94 hypogonadal men it was demonstrated that morning concentrations within the normal range could be produced. A total of 9% of observed patients stopped treatment due to chronic skin irritation or local contact dermatitis (Meikle, 1998). Absorption enhancers used in non-genital patches can cause topical irritation and/or allergic skin reactions (Jordan, 1997).

Pharmacokinetics were confirmed by a recent study in which subjects who were made artificially hypogonadal by the GnRH antagonist cetrorelix received transdermal trunk skin application systems at different doses. In 7% of the volunteers, contact dermatitis occurred at the site of the patch application (Rolf et al., 1999). Altogether, effects concerning sexual functions and prostate volume seem to match those achieved by conventional injection therapy (Meikle, 1998).

2.2.7.3. Transdermal testosterone gel. Recently, the pharmacokinetics of a transdermally applied 1% hydroalcoholic testosterone gel preparation were presented. For 14 days, eight hypogonadal men applied a 25-mg dose either four times to one site, or one time to four sites of the body; after 7 days subjects switched groups according to a cross-over design. Irrespective of application at one or four sites, serum testosterone levels rose to two- to three-fold, or four- to five-fold above baseline after 2 and 24 h after the first application. The serum levels remained stable at four- to 6.5-fold above baseline levels and returned to initial values 4 days after cessation of the treatment. Mean serum DHT levels followed the patterns shown for testosterone. Transdermal application of such a testosterone gel preparation at a dose of 100 mg/day could be an effective form of testosterone delivery to hypogonadal men (Wang et al., 1998).

2.2.8. 7α-Methyl-19-nortestosterone (MENT)

This potent androgen does not undergo 5α-reduction and is currently being investigated for clinical long-term use as an androgen substitute and as a contraceptive agent, since it is expected to have a lesser effect on the prostate. Initially tested in cynomolgus monkeys (Kumar et al., 1997), first tests in healthy men have been performed. Intramuscular injections caused peak levels after 1–2 h, causing significant drops in testosterone and gonadotropins. It seems to be a good candidate for implant administration (Suvisaari et al., 1997). MENT was shown to be ten times as potent as testosterone (measured as minimum LH suppression dose) when administered via minipumps to castrated monkeys (*Macaca fascicularis*). MENT had twice the effect on prostate growth as testosterone on these monkeys, thus given at a 1/10 of normal testosterone dose (which would be the adequate dose), it would only have half the impact on prostate growth. (Cummings et al., 1998).

3. Surveillance of testosterone substitution therapy

Monitoring testosterone therapy has several aspects: behavioural aspects, somatic properties and laboratory parameters have to be checked frequently. As testosterone is metabolised by 5α-reduction to 5α-dihydrotestosterone or by aromatisation to estrogens, the metabolic activity of these steroids should be taken into consideration as well.

3.1. Sexual behaviour, non-sexual behaviour, mood

Physical and mental activity, alertness and vigour can characterise sufficient replacement; low levels can be accompanied by lethargy, inactivity and depressed mood. Restitution of libido, increased sexual fantasies and the frequency of erections are markers of adequate therapy (Clopper et al., 1993; Morales et al., 1997).

3.2. Somatic properties

Following adequate testosterone substitution, most patients will report increasing frequency of shaving, some enjoy growing a beard for the first time. Hair growth in the upper pubic triangle will change to male patterns under substitution therapy. Muscles and physical strength are gained and as body weight increases in lean body mass, the fraction of fat will be diminished.

Initial gynecomastia can be caused by aromatisation to estrogens, especially during therapy with testosterone enanthate due to high peak levels. Adaption of the testosterone dose will cause gynecomastia to disappear.

As testosterone will briefly stimulate growth in hypogonadal patients with unfused epiphyses, followed by growth arrest, measurement of the bone age by X-ray of the left hand must be undertaken before initiating therapy (Nieschlag and Behre 1998).

3.3. Laboratory parameters

Testosterone levels are useful in judging the proper effects of substitution therapy, but the intrinsic pharmacokinetic profiles of different preparations must be considered. The time point of acquiring the sample is as important as the amount of time since the last injection/implant. In injection therapy, intervals rather than doses should be adjusted accordingly. DHT measurement is not required in routine cases, but if the patient does not respond properly, this parameter can be helpful in explaining a possible underlying deficiency in 5α-reductase.

Serum estradiol should be measured if high serum levels of testosterone occur, especially under treatment

with the enanthate ester and intervals should be prolonged if E_2 is too high.

Gonadotropins are of limited value as indicators, since they are decreased in hypogonadotropic hypogonadism and in Klinefelter patients often do not show significant reduction. Oral and transdermal testosterone may have no effect on LH.

Parameters of erythropoesis will increase as testosterone is a well-known stimulator of this system (Jockenhövel et al., 1997a). If too much testosterone is administered, a supraphysiological level can lead to polycythemia. In this case the dose has to be reduced to prevent patients from embolic or thrombotic events (Hajjar et al., 1997).

Standard coagulation parameters are not expected to change, whereas serum levels of proteins of the fibrinolytic system may alter. Increased thrombophilia has been reported in hypogonadal men due to higher levels of plasminogen-activator-inhibitor-type-1 (Winkler, 1996). Androgen substitution may decrease serum levels of this substance (Adamkiewicz et al., 1998). On the other hand, in numerous reports of steroid abusers dying of thrombotic events reference is made to testosterone action, as it may decrease cyclooxygenase activity in the vessel endothelium, and a lowering of levels of anti-aggregatory prostaglandins is assumed (von Eckardstein, 1998).

The testosterone metabolite 5α-DHT has been shown to increase human monocyte adhesion to human vascular epithelium in vitro, an effect that is most likely proatherogenic and is mediated by an increased expression of endothelial cell-surface adhesion molecules (McCrohon et al., 1999).

Lipid profiles may change; adverse effects such as decreasing HDL-levels and increasing LDL-levels have been reported in comparing different regimens in 55 hypogonadal men (Jockenhövel et al., 1999). On the other hand, beneficial effects were seen in a study which recruited especially elder hypogonadal men, as LDL levels decreased under testosterone substitution (Zgliczynski et al., 1996; for a complete review see von Eckardstein, 1998).

Elevated leptin as a possible link between energy metabolism and the gonadal axis is reduced by androgen substitution in hypogonadal men (Behre et al., 1997b; Jockenhövel et al., 1997b).

Liver function parameters should not alter under modern substitution therapy, since the toxic substances have vanished from treatment schedules and the proposed testosterone preparations do not show signs of liver toxicity. Under long-term use supraphysiological hormone levels may lead to an increment of serum transaminases in Asian men (Wu et al., 1996).

3.4. The prostate

Since the prostate is an androgen-sensitive organ and there has been much concern about induction of benign hyperplasia or carcinoma, this organ should be monitored closely. Testosterone increases prostate volume in hypogonadal men, but only to the extent of prostate size in age-matched controls (Behre et al., 1994). Transrectal ultrasound sonography and palpation belong to regular checkups and provide useful information (Behre et al., 1995a). Serum PSA levels must be checked regularly to detect a developing carcinoma. Uroflow measurements contribute to a complete picture of prostate function under testosterone substitution. Pathogenesis of benign prostate hyperplasia is probably mediated through the action of 5α-DHT. Over 90% of the testosterone entering the prostate is converted to 5α-DHT. This is a rather prostate-specific process and is not related to serum concentration of testosterone (Frick et al., 1998). Inhibiting 5α-reductase by finasteride can decrease prostate size (Stoner, 1994).

Androgens play a role in the development of prostate cancer, as it is almost never seen in hypogonadotropic patients or those with 5α-reductase deficiency and withdrawal of testosterone is used to cause prostate cancer to regress, suggesting that carcinoma cells are at least initially and partly dependent on androgens. This means that while testosterone can stimulate the growth of a prostate carcinoma, it cannot initiate it. To date, there is no evidence for high testosterone levels causing an increased rate of prostate cancer (Frick et al., 1998).

Since benign prostate hyperplasia and prostate cancer occur more often in elderly men, these patients must be examined carefully before and under testosterone substitution therapy.

4. Bone mass

As hypogonadism causes increased bone absorption and decreased mineralisation, it can lead to osteoporosis and, consequently, to fractures (Finkelstein, 1998). Replacing testosterone in hypogonadal patients will increase bone density (Behre et al., 1997c; Leifke et al., 1998). It is important to use testosterone preparations that can be converted into estrogen, since this hormone plays a significant role in bone metabolism (Nieschlag and Behre, 1998). Bone density should be measured in patients receiving testosterone substitution prior to treatment and regularly every 2 years.

Quantitative computer tomography (QCT) of the lumbar spine provides accurate information, other effective methods are dual photon absorptiometry and dual energy X-ray absorptiometry (Nieschlag and Behre, 1998).

5. Contraindications to testosterone treatment

Testosterone substitution stimulates growth of an existing prostate carcinoma, which has to be excluded before starting treatment and regular monitoring for this carcinoma is inevitable (Section 3.4).

Breast cancer is rare in men, and since it is estrogen sensitive, steroid treatment is a contraindication, though no cases of testosterone substitution followed by occurrence of breast cancer have been reported.

Testosterone suppresses spermatogenesis and should not be administered in patients who wish to father children.

Sexual offenders are sometimes treated by antiandrogenic therapy. Hence testosterone substitution could eventually lead to relapses, which would be a serious mistake.

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